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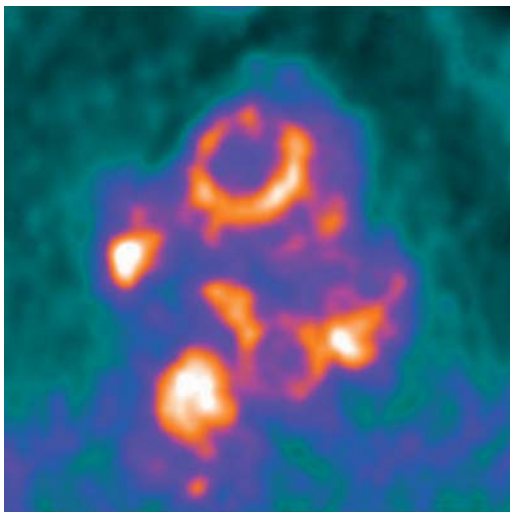

Inflame my plaque (inflammation and atherosclerosis)

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HEART AND METABOLISM

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Aim and Scope | *Heart and Metabolism* is a quarterly journal focusing on the management of cardiovascular diseases. Its aim is to inform cardiologists and other specialists about the newest findings on the role of metabolism in cardiac disease and to explore their potential clinical implications.
Each issue includes an editorial, followed by articles on a key topic. Experts in the field explain the metabolic consequences of cardiac disease and the multiple potential targets for pharmacotherapy in ischemic and non-ischemic heart disease.

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Inflammation in atherosclerosis: casualty or causality?

Michael Marber

The past 30 years have seen dramatic advances in molecular immunology resulting in the delivery of transformational disease-modifying therapies for rheumatoid arthritis and other ailments in which inflammation plays a pathogenic role. This therapeutic revolution has had little impact on our speciality, apart from highlighting that suppressing inflammation can increase the incidence of cardiovascular events! I find this surprising because inflammation is such a prominent histopathological feature of complex atherosclerosis; epitomized by the foam cell. The difficulty is we are still not sure if this inflammation is adaptive, maladaptive, or merely a bystander.

In reading through this issue I was reminded of a visit to Germany that coincided with an industrial accident during which toxic effluent had polluted the Rhine. There was an amusing anecdote circulating among my colleagues that the manager of the factory suspected of causing the accident had tried to blame the dead fish, "it's not our chemicals that have caused the damage but those stinking dead fish". This issue of *Heart and Metabolism* is grappling with a similar issue, are foam cells and other manifestations of inflammation merely dead fish?

A good place to start this issue is the article "Macrophages: cause or cure in atherosclerosis?" by Martin Bennett. The article provides a clear and concise overview of macrophage biology and highlights recent advances in our understanding of subtypes with specific properties. These macrophage subtypes may have diametrically opposing effects on atherosclerotic plaque progression, causing divergent findings and confusing the unwary. Complicating matters further is the ability of a macrophage to morph between types. Consequently, macrophages can both promote and prevent atherosclerotic plaque progression.

The other article that provides an improved understanding of basic immunology is the Refresher corner by Sidney Shaw on innate immunity. This article deals with the subject of sterile inflammation triggered by damage to normal cellular constituents. As a result of this damage, cellular lipids, proteins and nucleotides are changed to resemble those found in pathogens. These danger-associated molecular patterns are then recognized by the primitive innate immune system, principally through five families of receptors that are described in detail. The activation of these receptors then triggers a shared proinflammatory signalling network outlined in Figure 1. Once again it is unclear if such inflammation is harmful, and there seems little doubt that in many circumstances, such as immediately after acute myocardial infarction, it is required for tissue clearance and mature scar formation.

Despite the uncertain role inflammation plays in atherosclerosis much effort is being expended to image the vasculature in order to identify plaques vulnerable to rupture. Such plaques are metabolically active and this may manifest through high glucose utilization and/or active calcium deposition. These processes may be visualized using positron emitting 18F as a sodium salt (behaves like calcium) or covalently linked to deoxyglucose (behaves like glucose). Positron emission tomography lacks spatial resolution and does not highlight the adjacent "cold" tissue needed for anatomical interpretation of the images. As described in the article by Drs Joshi, Chowdhury and Rudd, this can be provided quickly and at high resolution by coincident computed tomography scanning. Such techniques are

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now being used as surrogate endpoints in clinical trials of agents that may protect against atherothrombosis as efficacy can be inferred in advance of the investment needed to deliver a phase III trial with relevant clinical endpoints such as myocardial infarction, stroke and the need for revascularization.

Such trials bring us nicely on to the articles “The role of inflammation in atherosclerosis: what we have learned from clinical trials" by M. Al-Hawwas and J.-F. Tanguay and “Secretory phospholipase: a potential target for cardiovascular therapies" by S. J. Nicholls and M. Duong. The article by Drs Al-Hawwas and Tanguay provides a comprehensive overview of phase II/III clinical trials currently being undertaken that involve anti-inflammatory strategies. The article by S. J. Nicholls and M. Duong is similar but concentrates on the phospholipase inhibitors. What is clear is that inflammation is a very active area of research, with a number of companies convinced it plays a pathogenic role in atherosclerosis. As explained by Drs Al-Hawwas and Tanguay, our current standard treatments, such as statins, probably work partly by suppressing inflammation. New agents would thus have to show benefit over and above the standard therapies that may already be acting on these pathways. Furthermore, as also discussed by Drs Al-Hawwas and Tanguay, standard anti-inflammatory drugs such as non steroidal anti-inflammatory drugs and prednisolone seem to increase, rather than decrease, cardiovascular risk.

I realise that the flavour of this Editorial is sceptical and questions the view that inflammation plays the role of bad guy in atherosclerosis. The best evidence for this comes from the Case report by Catriona Maybury and Catherine Smith and from the article by Malek Al-Hawwas and Jean-François Tanguay. Both sets of authors point out that chronic inflammatory disease is associated with accelerated atherosclerosis. This is best illustrated by allograft vasculopathy affecting the transplanted heart. Perhaps inflammatory cells are not that fishy after all? ■

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Macrophages: cause or cure in atherosclerosis?

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Abstract

Monocytes are a key cell type responsible for the generation of atherosclerosis. Monocytes/macrophages also play key roles in plaque growth and plaque instability. In contrast, recent research has demonstrated that macrophages can also suppress inflammation and promote healing and fibrosis. Some of this complexity relates to the presence of different macrophage subtypes that are induced and activated by different stimuli within the plaque. Macrophage functions include lipid uptake and oxidation with resultant foam cell formation, release of pro or anti-inflammatory cytokines, phagocytosis of dead macrophage and vessel wall cells, release of destructive enzymes such as matrix metalloproteinases, and presentation of antigen to immune cells. Each of these functions is likely to be occurring simultaneously in different subtypes within the complex environment of the plaque. While selective manipulation of monocytes/macrophages has clearly demonstrated their proatherogenic role in early plaque development, their role in advanced plaques has been more difficult to elucidate. Nonetheless, switching of a proinflammatory to an anti-inflammatory/reparative phenotype represents an attractive target for therapeutics in atherosclerosis. ■ Heart Metab; 2013;60:5–8

Keywords: Apoptosis; atherosclerosis; inflammation; macrophages.

Introduction

Macrophages are an almost constant feature in atherosclerosis, present from the earliest stages to advanced plaques. Macrophage invasion in response to retained lipoproteins, lipid accumulation and oxidation, inflammatory cytokine release, and their death have been viewed as major causes of atherosclerosis, and drivers of progression of established plaques. Indeed, reduction in monocyte numbers and prevention of monocyte ingress dramatically suppress atherogenesis [1]. These roles have resulted in the widespread view that macrophages are "bad news" in plaques, and the targets of both established and new therapeutics. Like many simplistic views, recent research has indicated that it is (at least partially) wrong. Macrophages can also be protective, particularly against ongoing inflammation and hemorrhage, which are major drivers for transition to an unstable plaque phenotype and plaque growth.

Macrophages: not one type, but many

Research over the past decade has found that circulating monocytes and macrophages in plaques consist of different types, whose role, regulation, markers and products differ [2]. In mice, hypercholesterolemia is associated with an increase in the inflammatory monocyte subset, known as Ly6c^{hi}, which can enter developing plaques readily. Although there are significant differ-

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Abbreviations

DC: dendritic cells; **GM-CSF**: granulocyte macrophage-colony stimulating factor; **IFN**: interferon; **IL**: interleukin; **M-CSF**: macrophage colony stimulating factor; **MHEM**: macrophage phenotype induced by hemoglobin–haptoglobin complexes; **MMP**: matrix metalloproteinase; **MOX**: macrophage phenotype induced by oxidized phospholipid; **ROS**: reactive oxygen species; **TGF**: transforming growth factor; **TNF**: tumor necrosis factor; **VSMC**: vascular smooth muscle cells

ences between monocyte subsets in humans versus mice, the Ly6c^{lo} subset is more associated with inflammation resolution [3]. Monocytes express a variety of chemokine receptors, cell surface selectins and integrins for migration and retention in atherosclerosis [1, 4]. Once within the plaque, monocytes differentiate into cells with macrophage or DC-like properties.

In atherosclerosis in humans, macrophages have been categorized into a variety of different types, based in part on the mechanisms underlying their activation and their proposed function. Therefore, a common classification of monocytes/macrophages is based on involvement in proinflammatory processes (M1, classically activated) versus those that undertake resolution of inflammation and repair (M2, alternatively activated) (see *Table I*) [5]. To these opposing functions other differences can be added, including primary involvement with innate or acquired immunity, tissue destruction or repair, immigration or emigration, and cholesterol accumulation or release. However, in-vitro studies suggest that these forms can be derived from the same precursors and can interchange, driven by specific growth/differentiation factors, T-helper type 1 and 2 cytokines, lipoproteins and lipids, and certain transcription factors [2] (see *Table I*). In addition, human plaques appear to contain macrophages with M1 or M2 phenotypes, but also intermediate phenotypes. This is not surprising given the complex environment of the plaque, but means that human plaque macrophages may not correspond to the phenotypes, markers and functions seen in vitro. Further complexities occur with the lack of definitive lineage markers, a mixture of lineage and activation markers, and the lack of functional evidence for each subset in vivo (reviewed in Johnson and Newby) [2]. In addition, further macrophage subtypes are present in plaques, including those arising by exposure to Mox, which can arise from both M1 and M2 types [6], and Mhem [7], often regulated through similar pathways. For example, both Mox and Mhem are regulated by the transcription factor Nrf2 [8].

Macrophage function in atherosclerosis

The diversity of macrophage subtypes in atherosclerosis is reflected in a huge diversity of function. Macrophage function ranges from lipid uptake and oxidation with resultant foam cell formation, release of pro- or anti-inflammatory cytokines, phagocytosis of dead macrophage and vessel wall cells, release of destructive enzymes such as MMP, and presentation of antigen to immune cells (reviewed in Moore and Tabas) [9]. The relative importance of each function depends on the model under study, and how advanced the plaques are. For example, in early atherogenesis, the

Macrophage type	Putative function	Increased by	Activation decreased by
M1 (classically activated)	Proinflammatory, secrete MMP	M-CSF, TNFα, IFNγ	IL-10, TGFβ
M2 (alternatively activated)	Anti-inflammatory, fibrosis, secrete IL-10 and TGFβ	GM-CSF, IL-4, IL-13	IL-10, TGFβ
Mox (activated by oxidized phospholipids) [6]	Decreased phagocytotic and chemotactic capacity	Oxidized phospholipids	
Mhem (activated by hemoglobin–haptoglobin complexes) [7]	Scavenge hemoglobin–haptoglobin complexes, reduced ROS release, increased survival, secrete IL-10	Hemoglobin–haptoglobin complexes, IL-10, heme oxygenase 1	

GM-CSF, granulocyte macrophage-colony stimulating factor; IFNγ, interferon γ; IL, interleukin; M-CSF, macrophage-colony stimulating factor; Mhem, macrophage phenotype induced by hemoglobin–haptoglobin complexes; MMP, matrix metalloproteinase; Mox, macrophage phenotype induced by oxidized phospholipid; ROS, reactive oxygen species; TGFβ, transforming growth factor β; TNFα, tumor necrosis factor α.

recruitment of inflammatory macrophages clearly drives atherosclerosis; thus blocking macrophage/endothelial cell interactions or reducing monocyte numbers/function inhibits atherogenesis. Unfortunately, in many studies these manipulations are systemic, while the chemokines/chemokine receptors are not specific for macrophages, making it difficult to be sure that effects are only mediated through macrophages.

Studies in established lesions are harder both to do and to interpret. Macrophages in these lesions are exposed to cholesterol crystals that have been shown in some studies to activate inflammasomes and promote inflammation [10, 11]. Macrophages can induce apoptosis of vascular smooth muscle cells (VSMC) by both ligand-dependent pathways and cytokine secretion [12], potentially reducing the covering fibrous cap and promoting plaque rupture. Macrophages can also reduce cap thickness by release of MMPs. Indeed, cap infiltration with macrophages is one of the most consistent features of human plaques that have ruptured [13]. Macrophages and VSMC are potent phagocytes, responsible for clearing debris and apoptotic cells within the "necrotic core". However, this "efferocytosis" is defective in advanced lesions [14], possibly by competition for phagocytic receptors by oxidized lipids [15]. Dead macrophages themselves contribute to the necrotic core, and thus macrophage death should promote core formation by both increased contribution and defective clearance. In contrast, if macrophages promote inflammation, then killing them might be protective in atherosclerosis. In fact, the literature in this area is contradictory (see Clarke and Bennett [16] for review), and recent evidence suggests that unlike VSMC death, macrophage death is not particularly proinflammatory [17]. Indeed, in most cases definitive evidence of the role of specific macrophage subtypes in vivo is lacking. This is partly because of the ability of different subtypes to interchange, the lack of specific markers that can be used to deplete them either from the circulation or plaque, and their rapid replenishment from the circulation [18]. It is also apparent that global increases or decreases in monocytes/macrophages both in the circulation and in the plaque can have different effects at different stages of the disease [18].

Role of dendritic cells in atherosclerosis

DC are immune cells that process and present antigen, leading to signals to adjacent T lymphocytes. DC are present both in normal vessel walls and in plaques, where some of them may derive from monocytes [4]. Plaque DC appear able to present antigen and activate plaque T cells [19], but also both to proliferate and form foam cells in early atherogenesis [20]. However, again their role is unclear, as targeted reduction leads to only modest effects in early lesions, or mixed effects in advanced plaques [19].

Conclusions

So what is the answer to the question posed at the beginning – Macrophages: cause or cure in atherosclerosis? The answer is probably both. In early lesions, the evidence that inflammatory macrophages promote atherosclerosis is overwhelming, particularly when plaque development is driven by hyperlipidemia. In advanced plaques the evidence is more mixed, and the situation in humans is complex, and does not necessarily correspond to that seen in mice or in human cells in vitro. The beneficial effects of statins in atherosclerosis are associated with a relative reduction in cells with macrophage markers in lesions; however, the relative effects of statins on different macrophage subtypes are unclear. The challenge for potential therapeutics is harnessing the reparative properties of macrophages to resolve inflammation in advanced lesions, while simultaneously reducing the ongoing recruitment of macrophages and their differentiation into a proinflammatory subtype. ■

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The role of inflammation in atherosclerosis: what we have learned from clinical trials

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Abstract

Drugs that modify the classic risk factors of atherosclerosis remain the mainstay of care. However, although effective, there is still a need for adjunctive therapies to reduce further the risk of subsequent cardiovascular events. In the search for new targets to achieve this incremental benefit over standard therapies, inflammation features prominently and has been implicated in atherosclerotic disease progression and cardiovascular morbidity in descriptive studies. Consequently, suppressing inflammation has been the focus of multiple clinical trials. Most of these phase II and III trials have shown promising, but not definitive, results. In addition, some trials have suggested that inflammation has a protective role, with anti-inflammatory interventions actually increasing the risk of cardiac events. Consequently, anti-inflammatory therapies have not impacted on clinical practice. In this article we review descriptive studies, such as those of the accelerated atherosclerosis that affects transplanted hearts, which suggest an inflammatory etiology to atherosclerosis. We then summarize key interventional clinical trials that have directly examined the inflammatory hypothesis. ■ Heart Metab; 2013;60:9–13

Keywords: Atherosclerosis; coronary artery disease; inflammation.

Introduction

Over the past 30 years there have been considerable achievements in the primary and secondary prevention of cardiovascular events in patients with known atherosclerosis and/or merely with risk factors for disease [1]. Despite these advances atherosclerotic disease remains the most frequent cause of death in high and middle income countries. This is partly the result of the inadequate implementation of known effective therapies. However, even in those patients optimally treated the risk of future events remains high, acting as an impetus to find new therapeutic targets. Key observations, such as the accelerated atherosclerosis that is seen in the transplanted heart (allograft vasculopathy) prove the concept that inflammation can act as a "soloist" in the pathophysiology of the disease. Quenching inflammation may thus prevent a silent preclinical atheroma from becoming symptomatic and/or reduce the risk of future events in those with established clinical disease. What is the evidence that this is the case?

Established therapies are anti-inflammatory

Hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) are very effective in reducing LDL cholesterol levels and cardiovascular events. Although these two factors are thought to have a cause–effect relationship, statins are also known to have an anti-inflammatory effect [2]. In numerous large scale trials,

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Abbreviations

hs CRP: high-sensitivity C-reactive protein; **IL-6**: interleukin-6; **LDL**: low-density lipoprotein; **MCP-1**: monocyte chemoattractant protein-1; **P38 MAPK**: P38 mitogen-activated protein kinase; **TNF**: tumor necrosis factor.

they have proved effective in primary and secondary prevention of atherosclerotic events [3]. This clinical benefit is also achieved when they are used to suppress inflammation (as measured by lowering high sensitivity [hs] C-reactive protein [CRP]) in otherwise healthy individuals with normal lipid profiles, as shown in the JUPITER trial [4]. In this large randomized controlled trial, treatment with a statin resulted in a 50% reduction in vascular events in ostensibly healthy people with elevated hs-CRP in the absence of dyslipidemia at enrolment. Statins lowered the levels of both LDL and hs-CRP; however, the absolute risk reduction in vascular events was related to CRP and not LDL. Furthermore, lowering CRP in groups of patients without classic cardiovascular risk factors, other than advanced age, resulted in a clinical benefit similar to that observed in high-risk patients. Statins may thus have additional anti-inflammatory properties revealed by their effect in patients with active systemic inflammation, as revealed by hs-CRP, although this conclusion of the JUPITER trial remains a subject of intense debate.

The possibility that the anti-inflammatory effect of statins may contribute to their efficacy, as raised by JUPITER and observations from other statin trials, has driven a critical examination of whether more traditional anti-inflammatory agents may have similar benefits, especially when the residual vascular risk remains elevated after control of cholesterol and hypertension. We next review the pharmacological agents studied in clinical trials to suppress inflammation.

Traditional anti-inflammatory drugs

Different conventional anti-inflammatory drugs targeting varied inflammatory pathways have been tested in patients with symptomatic and silent atherosclerotic disease.

Paradoxically, non steroidal and steroidal anti-inflammatory drugs have proved harmful in patients with atherosclerosis. In fact, except for acetyl salicylic acid, non steroidal anti-inflammatory drugs, especially selective cyclooxygenase 2 inhibitors, increase morbidity and mortality in patients with coronary heart disease [5, 6]. The cause of this increased risk is unknown but may relate to these agents promoting salt retention and thus elevating blood pressure or attenuating the antithrombotic function of the vascular endothelium. They may also antagonize the benefits of low-dose acetyl salicylic acid on platelet function. Initiated in 2006 and still actively recruiting, the PRECISION trial (NCT00346216) is comparing celecoxib, a selective cyclooxygenase 2 inhibitor, with two other non selective inhibitors in patients with, or at high risk of, cardiovascular disease.

Steroidal agents, the traditional potent immunomodulators, are a known cause of secondary dyslipoproteinemia and accelerated atherosclerosis. A current trial, however, is evaluating the effects of PEG-liposomal prednisolone sodium phosphate, on atherosclerotic plaque inflammation as measured by positron emission tomography–computed tomography imaging (NCT01601106).

Colchicine is another anti-inflammatory drug that inhibits the expression of adhesion molecules on T cells and endothelial cells, the synthesis of TNF and interleukin (IL)-6 and the secretion of metalloproteinase 9. It has been used successfully to block inflammation in gout and pericarditis, and is currently being investigated for other cardiovascular indications. In a clinical study, colchicine was found not to differ from placebo in suppressing inflammatory markers (hs-CRP) in patients with acute coronary syndrome or stroke [7], whereas low-dose colchicine (0.5 mg/day) was effective in the secondary prevention of cardiovascular events in patients with stable coronary disease in another study [8].

Early observational data from patients with rheumatoid and psoriatic arthritis suggest that anti-inflammatory agents used in these inflammatory disorders can result in a concomitant reduction in the risk of cardiovascular disease. Patients taking methotrexate, a drug with multiple molecular and cellular inflammatory targets, had an 18% lower risk of myocardial infarction and a 21% reduction in total cardiovascular disease in a meta-analysis of multiple rheumatoid/psoriatic arthritis studies [9].

On the basis of these previous results, a prospective randomized large scale study has just been initiated to examine if suppressing inflammation with low-dose methotrexate (15–20 mg/week) will lower the rate of major cardiovascular events (myocardial infarction, stroke and cardiovascular death) in patients

with known stable coronary artery disease/post myocardial infarction who also have one of the known common proinflammatory diseases: diabetes mellitus type 2 or metabolic syndrome. The study, the Cardiovascular Inflammation Reduction Trial (CIRT), is one of the major clinical studies interrogating the inflammatory hypothesis of atherosclerosis against the background of optimal medical therapy, therefore it should provide information on whether this is a viable additional target.

Antioxidants

Oxidation of lipoproteins in the arterial wall is one of the early processes in atheroma formation that is thought to act as a stimulus for the innate and adaptive immune responses driving inflammation. However, reactive oxygen and nitrogen species also play a role in causing endothelial dysfunction, which may contribute to atherosclerosis independent of inflammation. Therefore, blocking oxidative stress is theoretically attractive in primary and secondary prevention. Furthermore, statins and angiotensin converting enzyme inhibitors have known antioxidative effects that may contribute to their efficacy. Despite this apparent solid theoretical foundation, classic antioxidative agents such as vitamins E, A and C hold no clinical benefit over placebo in well-controlled and randomized trials, a conclusion reinforced in a large meta-analysis [10].

Another antioxidative agent, succinobucol, the monosuccinic acid ester of probucol, which inhibits TNF-inducible expression of different adhesion molecules (vascular cell adhesion molecule 1, monocyte chemoattractant protein-1 and E-selectin), has also failed in one study [11] to lower the primary composite outcome of cardiovascular death, resuscitated cardiac arrest, non fatal myocardial infarction, non fatal stroke, unstable angina, or coronary revascularization. However, succinobucol was associated with a small but significant reduction in the clinical burden of atherosclerosis that excluded unstable angina and coronary revascularization. The drug had a favorable effect on glucose control and noticeably lowered the incidence of new-onset diabetes mellitus.

Interleukin inhibitors

The role of interleukins as inflammatory modulators in chronic collagen vascular diseases is well established. While IL-1, IL-6 and TNF are known proatherosclerotic mediators, IL-10 and transforming growth factor have anti-inflammatory properties. In atherosclerosis, IL-1 seems to play a role in plaque initiation, instability and subsequent clinical events [12].

The successful clinical application of antagonists of proinflammatory interleukins (mainly IL-1) in rheumatoid arthritis has inspired their use in patients with atherothrombotic disease. Currently, three agents have progressed to phase II (anakinra and rilonacept) or phase III clinical studies (canakinomab) for atherosclerosis.

Canakinomab is a humanized monoclonal antibody to IL-1β, which is being evaluated in a large scale randomized controlled trial (the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study [CANTOS]; NCT01327846) in patients with previous myocardial infarction who have active persistent inflammation as measured by elevated hs-CRP. The study (CANTOS) is expected to be completed in 2016 and will demonstrate whether cardiovascular events (recurrent myocardial infarction, stroke and cardiovascular death) can be reduced by canakinomab. In common with the CIRT trial (see above) the placebo group includes optimal secondary prevention therapies. At the same time, the incidence of other disorders in which inflammation may play a pathogenic role such as diabetes mellitus, atrial fibrillation and thromboembolism will be co-interrogated.

Leukotriene inhibitors

Leukotrienes are arachidonic acid derivatives synthesized through the 5-lipoxygenase enzyme pathway. They potentially contribute to the atherosclerotic process through vasoactive effects and/or direct cellular action (on endothelial, vascular smooth muscle and circulating mononuclear blood cells). Aside from their role in the preclinical phase of the disease they have been found to associate with plaque instability and rupture [13].

Leukotrienes have been blocked by either targeting their synthesis (inhibition of the 5-lipoxygenase enzyme or one of the other key enzymes of the leukotriene synthetic pathway) or by blocking their receptors (cysteinyl leukotriene 1 receptor). VIA 2291, an inhibitor of 5-lipoxygenase, was shown to decrease inflammatory markers and unstable plaque burden, as evaluated by the volume of non calcified plaques on multislice coronary computed tomography angiography in patients with recent acute coronary syndrome [14]. Furthermore, montelukast, a leukotriene receptor antagonist, was found in a retrospective observational study to be associated with a lower incidence of my-

ocardial infarction in men and a lower incidence of stroke in both men and women who used this drug to control their asthma [15].

p38-MAPK inhibitors

This enzyme has pleiotropic biological functions including the initiation and progression of atherosclerosis in animal models. Losmapimod is a selective inhibitor of the alpha and beta isoforms of p38-mitogen-activated protein kinase (MAPK) that has been studied in patients with clinically stable atherosclerotic disease. Losmapimod was shown in this placebo-controlled study to lower inflammatory markers (hs-CRP) and to decrease inflammation, as measured by [^{18}F]2-fluoro-2-deoxyglucose positron emission tomography/computed tomography imaging, in the aorta and carotid arteries [16].

The positive effect of losmapimod on inflamed atherosclerotic plaques in the aorta and carotids encouraged a trial in non-ST-segment elevation myocardial infarction, SOLSTICE (NCT00910962) (the Study of Losmapimod Treatment on Inflammation and Infarct Size) [17]. This recently completed phase IIb placebo-controlled trial revealed promising signals on inflammation (CRP), other biomarkers such as brain natriuretic peptide and infarct imaging endpoints, leading to an upcoming phase III trial.

P-selectin antibodies

P-selectin is one of the adhesion molecules expressed on the surface of endothelial cells and platelets. It facilitates the recruitment of inflammatory cells (mononuclear and T lymphocytes) to the arterial wall in inflammation, atherothrombotic disease, and vascular healing [18–20].

Therapeutic antibodies blocking P-selectin have been studied in separate trials in two settings: SELECT–ACS and SELECT–CABG. In first study, SELECT–ACS, the P-selectin antibody, inclacumab, was compared to placebo in non-ST-segment elevation myocardial infarction patients undergoing percutaneous coronary intervention. Inclacumab resulted in a smaller area of myocardial damage as measured by serum troponin and creatine kinase myocardial type at 16 and 24 hours post procedure [21]. The other ongoing study, SELECT–CABG, is examining whether inclacumab lowers venous conduit disease during the first year following coronary artery bypass graft surgery.

Conclusion

Accumulating evidence suggests blocking inflammation in atherosclerosis could complement standard cardiovascular prevention to reduce further the risk of future events. However, this evidence is not conclusive and is best viewed as work in progress. Consequently, the only drugs currently recommended are the traditional agents such as statins and angiotensin converting enzyme inhibitors that include an anti-inflammatory action among their many pleiotropic effects. The results of two important proof-of-concept trials discussed above (CIRT and CANTOS) are eagerly awaited. Furthermore, confirmation of the benefits of p38-MAPK inhibitors and P-selectin antagonists may be forthcoming over the next few years. Until the results of such phase III studies are revealed, the pathogenic role of inflammation in human atherosclerosis remains uncertain. ■

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Heart Metab. (2013) 60:15-21

Metabolic imaging: imaging plaques

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Abstract

Atherosclerosis is an inflammatory disease that causes most myocardial infarctions. Able to highlight areas of high glucose metabolism, PET imaging using FDG has been advocated as a means of measuring inflammation in the arterial wall. FDG uptake is correlated with the number of cardiovascular risk factors, and emerging evidence suggests that it may play a role in the prediction of risk for future cardiovascular events. While the determinants of vascular FDG uptake are still the focus of study, this imaging technique is reproducible and is increasingly being used to test novel anti-atherosclerotic drugs in phase II clinical trials. This review will outline the evidence base, shortcomings and emerging applications for FDG-PET in vascular imaging. Alternative, potentially more specific, PET tracers for measuring vascular inflammation will also be discussed. ■ Heart Metab; 2013;60:15–21

Keywords: Atherosclerosis; fluorodeoxyglucose; inflammation, non invasive imaging.

Introduction

Non invasive imaging of atherosclerosis ideally aims to provide novel insight into the underlying biology of the disease, a means to track the effects of drug therapies and value in the assessment of at-risk individuals.

PET is attractive because of its molecular sensitivity; picomolar levels of tracer can be detected at a target site, though spatial resolution is limited (3–5 mm). Co-registration with CT or MRI is needed to localize PET tracer uptake to underlying anatomy. PET imaging involves ionizing radiation, precluding its use for population screening. Nevertheless, imaging with FDG-PET has made considerable progress towards the above goals. This review will outline the evidence for its use in clinical imaging.

Imaging inflammation with FDG

FDG, a glucose analogue, competes with endogenous glucose for facilitated transport sites and after phosphorylation becomes trapped within cells. This accumulation can then be imaged and quantified in the PET scanner. FDG-PET is the gold standard imaging modality for the detection of tumor metastases in oncology, wherein it exploits the higher metabolic demands of cancer cells. Vascular FDG uptake was thus first noted in patients undergoing PET for cancer staging [1]. FDG is the most commonly used tracer in PET imaging of atherosclerosis. Although uptake is not specific for inflammatory cells, it exploits the fact that macrophages have higher glucose metabolism than both surrounding cells and healthy artery wall [2].

Imaging protocols and analysis

Techniques and methods of image analysis of FDG-PET for atherosclerosis have not yet been standardized [3]. Patients are required to fast before imaging. [^{18}F] has a half-life of 110 minutes, and a typical dose of approximately 250 MBq is injected intravenously and allowed to circulate. The circulation time (90–180 minutes) is generally longer than for oncological examinations to allow for accumulation into the diseased vascular wall and adequate clearance of blood pool activity, creating favourable TBR [4] (*Figure 1*).

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Abbreviations

BMI: Body Mass Index; **Bq:** Becquerel; **CT:** Computed Tomography; **DOTATATE:** [1,4,7,10-tetraazacyclododecane-N, N', N", N""-tetraacetic acid]-D-Phe1,Tyr3-octreotate; **FDG:** [18F]-2-fluoro-2-deoxyglucose; **MI:** Myocardial Infarction; **MRI:** Magnetic Resonance Imaging; **PET:** Positron Emission Tomography; **SUV:** Standardized Uptake Value; **TBR:** Target-to-Background Ratio; **TIA:** Transient Ischaemic Attack

Different methods have been proposed to quantify FDG uptake in atherosclerosis. The SUV, which is the decay-corrected tissue concentration of FDG (in kBq/g), corrected for injected FDG dose and lean body mass, is a widely accepted method that does not require plasma sampling. Correction (by division) for blood pool (venous) activity produces a TBR. TBR has been shown to correlate better with underlying macrophages than maximum SUV [5].

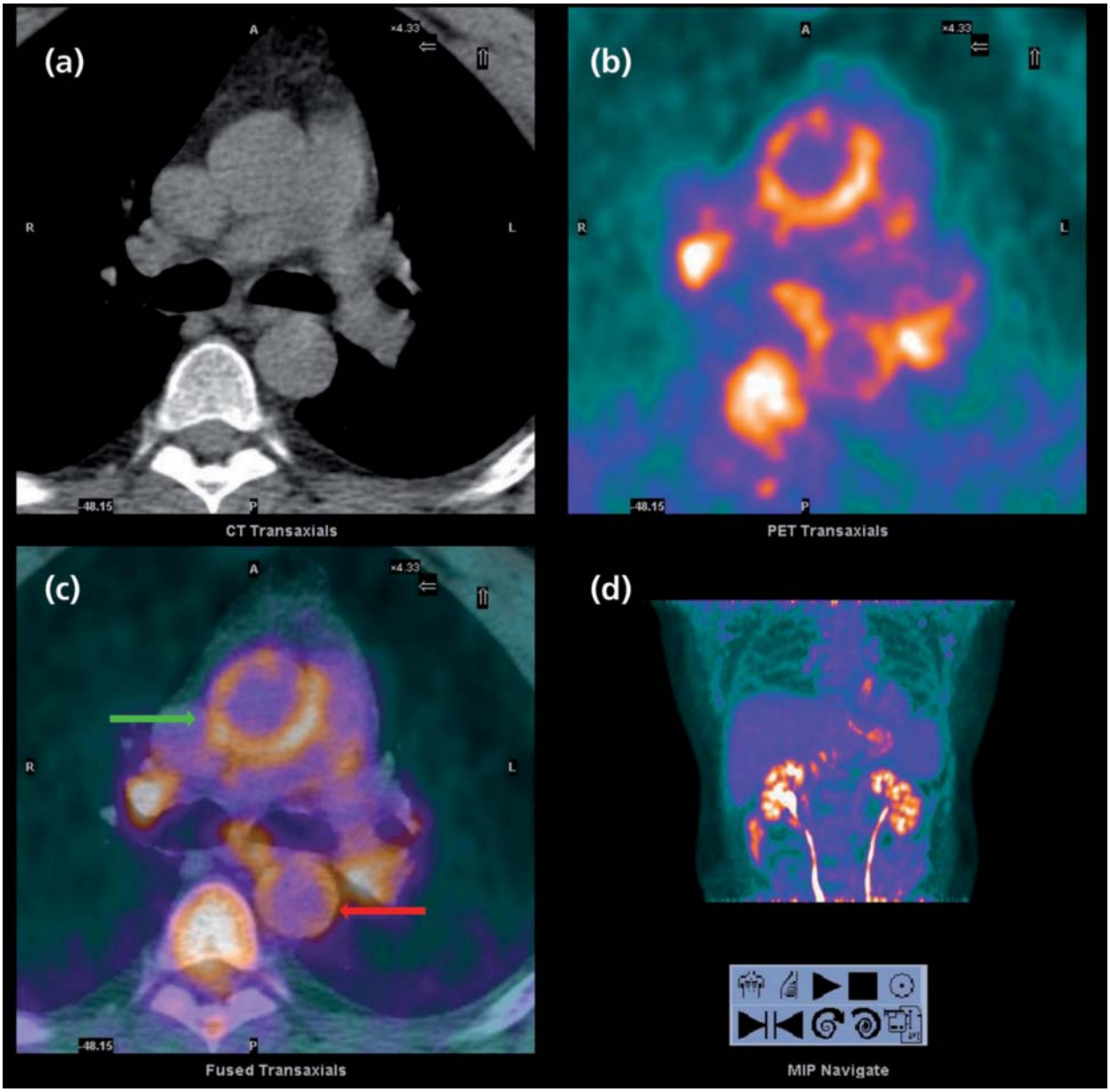

Fig. 1 *Imaging vascular inflammation with FDG-PET/CT. (a) Transaxial CT image of the ascending aorta at the level of the main pulmonary artery. (b) Corresponding transaxial FDG-PET image at the same location. (c) Fused PET/CT image allowing for anatomical co-localization of FDG uptake. Circumferential uptake is noted in both the ascending aorta (green arrow) and the descending aorta (red arrow). (d) Coronal FDG-PET image in the same patient. There is relatively little myocardial uptake in this case, while renal excretion of the tracer is noted. CT, computed tomography; FDG, [^{18}F]-2-fluoro-2-deoxyglucose; PET, positron emission tomography.*

Imaging human atherosclerosis with FDG

In the first prospective study in humans, levels of inflammation measured as accumulation rate of FDG were 27% greater in the culprit carotid after recent stroke or transient ischemic attack (TIA) than in the contralateral vessel [6] (*Figure 2*). Ex-vivo imaging by micro-PET (resolution 1 mm) has confirmed heterogeneous uptake within carotid plaques, with "hot spots" of uptake co-localizing with regions of intense macrophage infiltration [7]. FDG uptake is independent of plaque thickness, area or luminal stenosis [5] and is linked to male sex, age, smoking, the metabolic syndrome [8] and type 2 diabetes [9] (*Figure 3*). FDG-PET is a reproducible measure, valid across several vascular beds with excellent short-term and interobserver reproducibility [10].

There is evidence that plaque metabolic activity correlates with high-risk anatomical features within atherosclerotic plaques. Large lipid cores on carotid MRI and increasing numbers of high-risk markers (low attenuation plaque, surface irregularity and positive remodeling) on carotid CT angiography have higher FDG uptake than more stable phenotypes [11, 12]. FDG uptake can distinguish between culprit carotid and vertebral lesions in posterior circulation stroke [13], and in the carotid artery uptake correlates with microembolic signals on transcranial Doppler ultrasound after TIA [14].

Determinants of vascular FDG uptake

Autoradiography with tritiated deoxyglucose was shown to co-localize with macrophages in explanted carotid plaque [6]. Tawakol et al [5] demonstrated a very strong correlation of in-vivo imaging with macrophage staining, and suggested that uptake was independent of smooth muscle cell content. FDG uptake is thought to reflect activation status of macrophages; recent in-vitro data suggest that increased uptake may reflect early foam cell development [15].

However, both the cellular microenvironment and delivery of tracer via intraplaque neovessels [16] are also likely to be important contributors to the observed signal. Hypoxia is known to exist within atherosclerotic plaques [17]. Hypoxia leads to increased glycolysis, up-

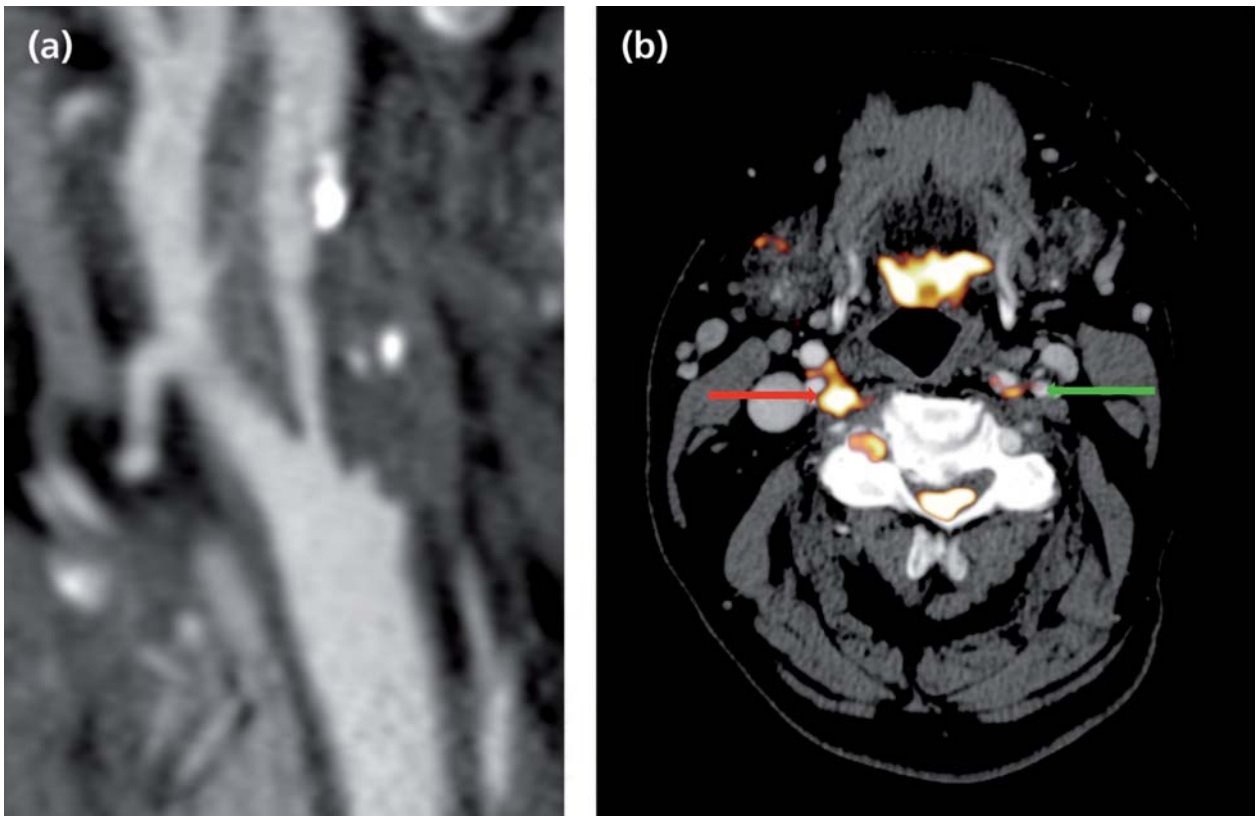

Fig. 2 *FDG-PET/CT imaging in symptomatic carotid atherosclerosis. (a) CT angiography: three-dimensional multiplanar reformatted image of a severely stenosed right internal carotid artery 1 week after an acute cerebrovascular event in a 69-year-old man. (b) FDG-PET: transaxial image of PET co-registered to CT angiography in the same patient. Intense tracer uptake is noted in the culprit right internal carotid artery (red arrow). Lesser uptake is noted in the left internal carotid artery (green arrow). CT, computed tomography; FDG, [^{18}F]-2-fluoro-2-deoxyglucose; PET, positron emission tomography.*

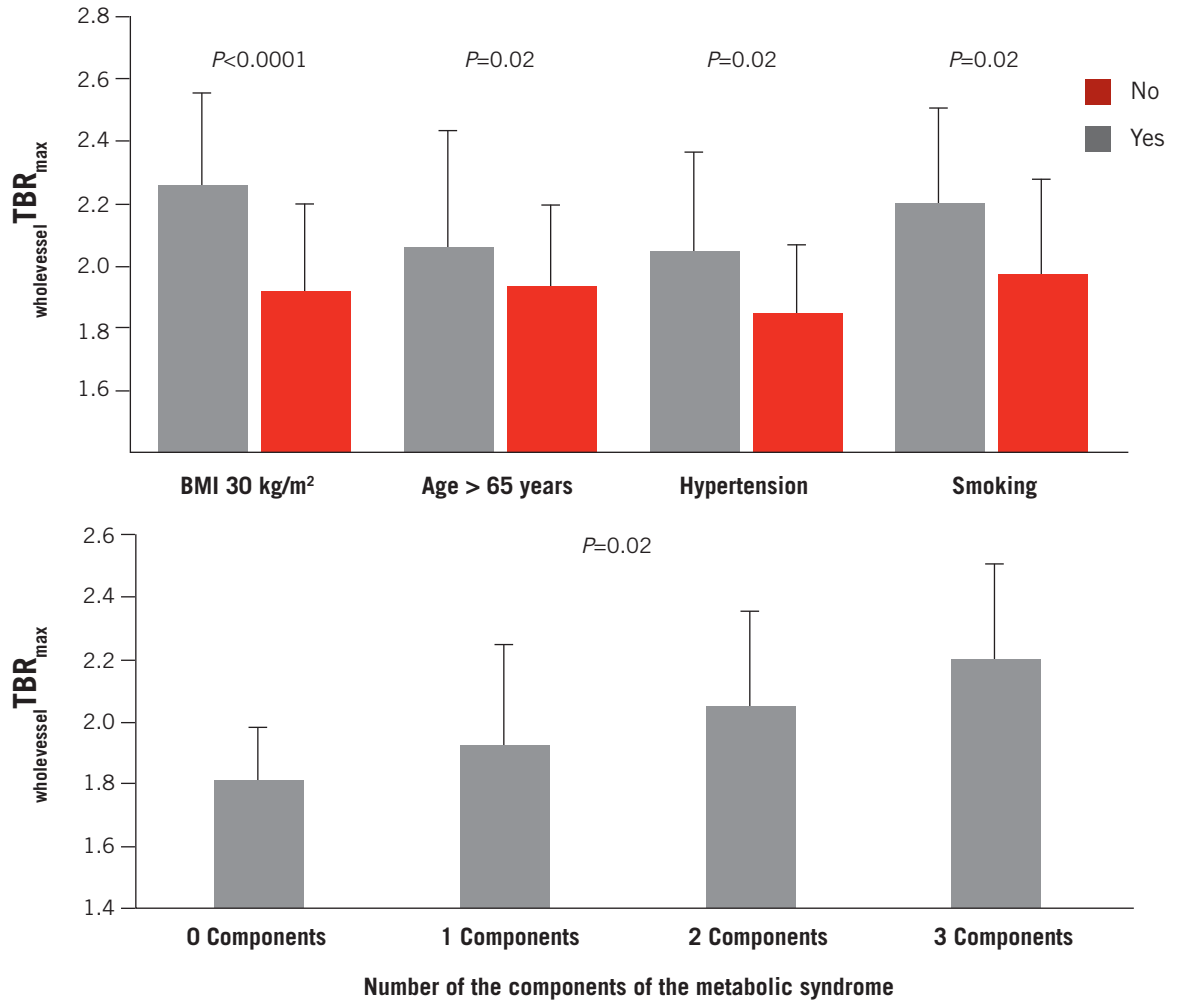

Fig. 3 *Vascular risk factors and carotid arterial FDG uptake. (a) Clinical risk factors and carotid vessel wall inflammation in patients with coronary artery disease. The presence of a body mass index of 30 kg/m2 or greater, age greater than 65 years, hypertension and smoking are independent predictors for the maximum whole-vessel TBR (wholevesselTBRmax). (b) Relationship between the components of the metabolic syndrome and the same measure of carotid arterial FDG uptake. BMI, body mass index; FDG, [18F]-2-fluoro-2-deoxyglucose; TBR, target-to-background ratio. (From Bucerius et al [8] with permission).*

regulation of glucose transporters, promotes the development of foam cells [18], adversely affects macrophage lipid metabolism [19], and drives neoangiogenesis and further inflammatory responses, all of which may influence in-vivo FDG imaging [20]. Further studies are required for clarification of how important these effects are in clinical imaging.

Intervention studies with vascular FDG imaging

Because of the central role of inflammation in atherosclerosis, and the number of therapies that aim to reduce it, increasingly, arterial FDG-PET/CT imaging is being applied for the early assessment of anti-atherosclerosis therapy. Treatment with statins demonstrated signal reduction after only 3 months' therapy [21]. The recent dal-PLAQUE trial with dalcetrapib has further demonstrated the value of FDG-PET for this purpose, providing evidence of vascular safety (ie, no increase in inflammation) versus placebo at 6 months with this novel agent [22].

Coronary artery imaging

Imaging coronary artery atherosclerosis presents special challenges. These arteries are smaller than the resolution of PET. Imaging is hindered by respiratory and cardiac motion during the time taken to acquire a PET dataset, typically around 20 minutes. Finally, FDG is taken up avidly by myocardium, which preferentially metabolizes glucose over free fatty acids.

Attempts to switch myocardial metabolism to free fatty acids by dietary manipulation before imaging have had varying success. In a study of [18F]-sodium fluoride

and FDG uptake in the coronary arteries of patients with aortic stenosis, and using overnight fasting to suppress myocardial uptake, only 50% of coronary segments were analyzable [23]. By gating for cardiac motion, in addition to dietary manipulation, fasting and intravenous heparin, Cheng et al [24] were able to demonstrate increased culprit site FDG uptake more commonly in patients with acute MI than in patients with stable angina. However, even this approach failed to suppress myocardial FDG uptake adequately in 11 of 27 patients and failed to detect increased signal at the culprit site in nearly half of patients after MI [24]. It seems likely that imaging inflammation in coronary plaques will require more macrophage-specific tracers than FDG.

Molecular imaging of vascular inflammation: alternatives to FDG

Many promising tracers already have applications in oncology. These include radiolabeled choline, taken up and integrated into cell membranes in tumor cells and macrophages. [11C]-choline was not taken up into normal vascular wall, or purely calcified lesions, in a retrospective analysis of 93 male patients undergoing cancer imaging [25].

Coronary artery uptake has been described for the somatostatin receptor analogue [68Ga]-DOTATATE in the left anterior descending coronary artery, correlating with previous cardiovascular events [26]. More recently, a retrospective study of cancer imaging has demonstrated [^{68}Ga]-DOTATATE uptake in large arteries, including the carotids, correlating with the presence of calcified plaques, age, hypertension and vascular FDG uptake [27]. Concordant vascular uptake of both tracers was only seen in a minority of the cases reviewed, and it has been suggested that this may reflect greater specificity of [^{68}Ga]-DOTATATE for proinflammatory macrophages (*Figure 3*). Further studies are awaited.

Prognostic implications of vascular FDG uptake

In retrospective analyses of patients undergoing PET for oncology staging, high levels of baseline vascular FDG uptake were associated with subsequent cardiovascular events [28]. In a prospective series of 60 patients after TIA and stroke, Marnane et al [29] have shown that uptake of FDG into carotid plaque predicts recurrent stroke independently of the degree of stenosis (*Figure 4*). The authors were able to define thresholds of FDG uptake to identify accurately the risk of recurrent stroke: maximum SUV values greater than 3.33 conferred a 14-fold increase in the accuracy of the clinical estimate of this outcome. In addition, because some of these patients will have undergone endarterectomy, it is likely that this figure represents an underestimate of the predictive power of FDG-PET. These data need further validation but suggest FDG may play a role in the selection of candidates for endarterectomy.

The results of prospective event-driven studies are awaited, including the BioImage Study that aims to identify imaging markers (CT, MRI and FDG-PET/CT) of future cardiovascular risk in asymptomatic patients [30].

Conclusions

Non invasive imaging of atherosclerosis is needed to investigate the underlying biology, identify at-risk individ-

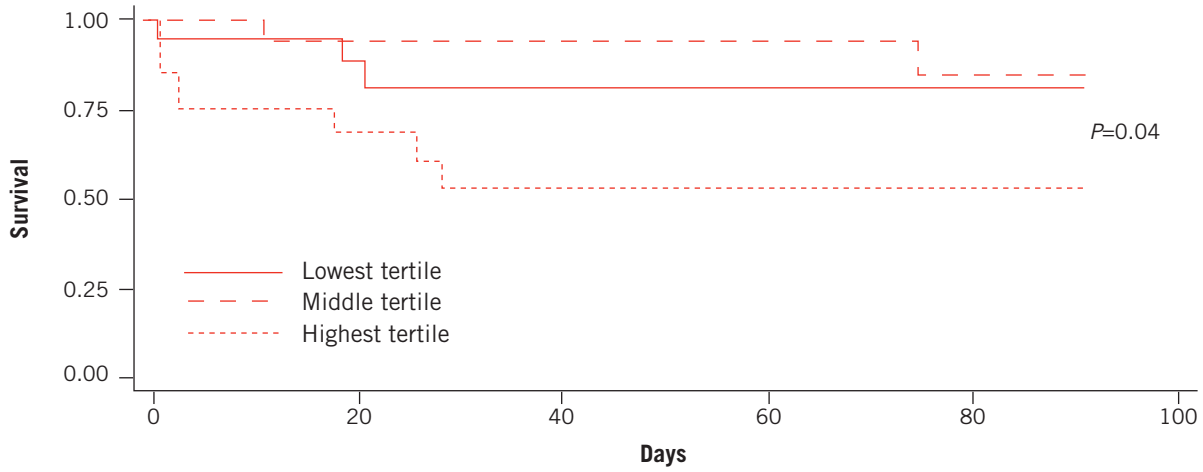

Fig. 4 *FDG imaging of culprit carotid arteries predicts recurrent stroke. Kaplan–Meier survival estimate (freedom from recurrent stroke) by tertiles of maximum standardized uptake. FDG, [18F]-2-fluoro-2-deoxyglucose. (From Marnane et al. [29] with permission).*

uals and test novel anti-atherosclerotic therapies. Vascular imaging with FDG in both preclinical models and human subjects has provided considerable insight into pathophysiology. The technique is reproducible enough to test new treatments in phase II clinical trials. Nevertheless, its main limitation, namely a lack of specificity, is acknowledged. Ongoing work will define the extent to which hypoxia is a determinant of the observed uptake into atherosclerotic plaque. More specific tracers will probably be needed to image inflammation in the coronary circulation.

Finally, although prospective data regarding its value for risk prediction are awaited, the ionizing radiation associated with vascular PET imaging will probably limit its application for widespread screening of asymptomatic individuals. ■

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Heart Metab. (2013) 60:22-26

Secretory phospholipase: a potential target for cardiovascular therapies

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Abstract

Increasing evidence implicates the activation of inflammatory pathways in the pathogenesis of cardiovascular disease. Accordingly, there is considerable interest in the development of new cardioprotective therapies that target inflammatory factors that promote the progression of heart disease. Secretory phospholipase A_2 ($sPLA_2$) generates a range of fatty acid and prostaglandin metabolites that play a pivotal role in the molecular events involved in the formation, progression and rupture of atherosclerotic plaque. The findings of $sPLA_2$ in atherosclerotic plaque, accelerated disease in transgenic models and association between elevated $sPLA_2$ levels in plasma and adverse cardiovascular events in population studies suggest that the pharmacological inhibition of $sPLA_2$ may be beneficial. The early experience with the clinical development of $sPLA_2$ inhibitors to reduce cardiovascular risk will be reviewed. ■ Heart Metab; 2013;60:22–26

Keywords: Cardiovascular disease, inflammation, risk factor, $sPLA_2$.

Introduction

Randomized clinical trials have demonstrated that targeting established risk factors such as cholesterol and blood pressure reduce cardiovascular event rates. While this has led to a profound reduction in coronary mortality rates, there remains a substantial residual risk of clinical events [1]. This supports the need to develop more effective strategies to achieve more effective reductions in cardiovascular risk. The discovery of factors involved in the pathogenesis of cardiovascular disease provides potential targets for the development of novel cardioprotective agents.

Role of inflammation in atherosclerosis

Increasing evidence supports the concept that atherosclerosis is a chronic inflammatory process. Migration of leukocytes from the circulation into the artery wall represents one of the earliest features of plaque formation. Ongoing accumulation of inflammatory cells within plaque promotes formation of the mature atherosclerotic plaque and its rupture, the underlying pathological event leading to acute ischemia [2]. This is supported by reports that circulating inflammatory markers predict adverse cardiovascular outcomes in population studies [3] and that reductions in these levels are independently associated with the clinical benefit of established therapies [4, 5]. There remains considerable interest in the development of novel agents that primarily target inflammatory mediators of the disease process.

Role of $sPLA_2$ in atherosclerosis

Phospholipases hydrolyze the sn-2 ester bond in phospholipids in cell membranes and circulating lipoprotein particles generating fatty acid, arachidonic acid, prostaglandin and leukotriene metabolites involved in the promotion of inflammatory pathways (see *Figure 1*). Five distinct groups of phospholipase A_2 (PLA_2) enzymes have been described, with their true physiological role in humans is yet to be elucidated. The forms of secretory ($sPLA_2$) and lipoprotein-associated (Lp-

Abbreviations

CRP: C-reactive protein; **LDL:** low-density lipoprotein; **PAF:** platelet activating factor; **sPLA2:** secretory phospholipase A2

PLA_2) forms of the enzyme have been most extensively studied with regard to their potential role in atherosclerotic cardiovascular disease [6–8].

The various subtypes of $sPLA_2$ have numerous functional properties that activate immune and inflammatory pathways [9], with a well-documented role in a range of systemic inflammatory processes [10–12]. Increasing evidence has implicated $sPLA_2$ in the formation, progression and rupture of atherosclerotic plaque, including co-localization with macrophages and smooth muscle cells [13], and mechanistic studies demonstrating that $sPLA_2$ promotes the generation of atherogenic small, dense LDL particles and phospholipid products in the artery wall that upregulate the activity of inflammatory and oxidative pathways [14, 15]. The transgenic expression of $sPLA_2$ results in a greater extent of atherosclerotic plaque in mouse models [16], supporting the atherogenic properties from mechanistic studies. Beyond a potential role of $sPLA_2$ in the progression of atherosclerotic disease, additional reports implicate activity in ischemia–reperfusion tissue injury. The direct binding of $sPLA_2$ to ischemic cardiomyocytes focuses inflammatory and oxidative-induced cellular damage, providing a potential further role in the events that link atherosclerosis and its adverse clinical sequelae [17].

Evidence implicating $sPLA_2$ in heart disease in humans

Further evidence associating $sPLA_2$ with cardiovascular disease has been derived from numerous population studies that demonstrate a direct relationship between systemic levels of $sPLA_2$ mass and activity with adverse cardiovascular events. $sPLA_2$ levels have been demonstrated to be greater in the setting of obesity, and consistent with mechanistic studies, to correlate directly with systemic levels of small LDL particles and oxidized LDL [18]. This translates to findings from large cohort studies, spanning the full spectrum of cardiovascular risk, which demonstrate an association between elevated $sPLA_2$ levels and the prospective risk of cardiovascular events.

In studies of asymptomatic individuals with no overt evidence of cardiovascular disease, $sPLA_2$ mass predicted the subsequent likelihood of a cardiovascular event, independent of traditional risk measures [19]. The observation of independence of this relationship from measures of apolipoprotein B is in contrast to sim-

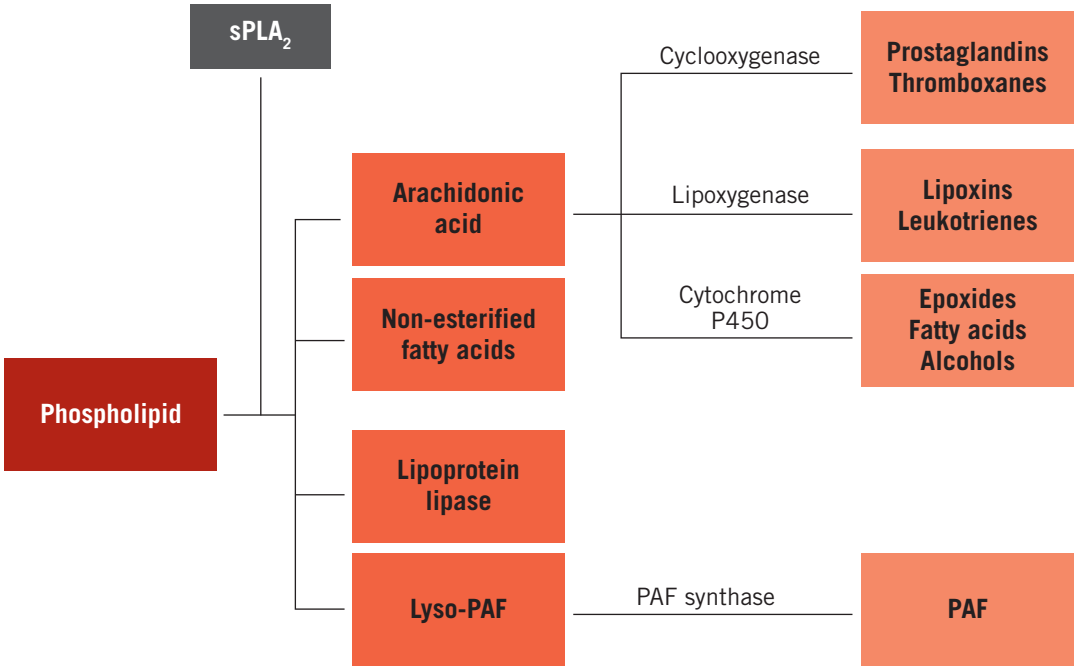

Fig. 1 *Role of secretory phospholipase in the generation of phospholipid byproducts. PAF, platelet activating factor; $sPLA_2$, secretory phospholipase.*

ilar associations reported for Lp-PLA_2, which cannot be completely dissociated from measures of atherogenic lipoproteins. Similar findings of a relationship between $sPLA_2$ levels and subsequent cardiovascular events have been reported in patients with either stable [19] or unstable [7] ischemic syndromes. In the coronary care setting, $sPLA_2$ levels have been demonstrated to increase in the first few days in association with the degree of myocardial damage [20]. Furthermore, increases in $sPLA_2$ levels have been observed following percutaneous coronary interventions, with the degree of increase associating with the subsequent risk of ischemic events due to either the progression of native atherosclerosis or the development of in-stent restenosis [21, 22].

Early experience with $sPLA_2$ inhibition

On the basis of preclinical studies and findings from population cohorts implicating a role for $sPLA_2$ in the pathogenesis of cardiovascular disease, there has been considerable interest in the development of pharmacological $sPLA_2$ inhibitors to reduce cardiovascular risk. Varespladib is the first $sPLA_2$ inhibitor to proceed to an advanced stage of clinical development. Initially developed as a potential therapeutic agent for asthma patients, subsequent studies focused primarily on its potential cardioprotective effects. In the form of a prodrug, varespladib is converted to its active form by plasma esterases that hydrolyze carboxylic acid. Preclinical studies in mouse models have demonstrated that varespladib had a favorable effect on both the size and composition of atherosclerotic lesions, when administered as monotherapy or in combination with a statin [23]. The potential ability to stabilize plaque, in addition to more chronic effects on the vasculature, suggested that $sPLA_2$ inhibition with varespladib might be beneficial in patients with an acute coronary syndrome.

A number of early clinical studies in patients with coronary artery disease provided further evidence to support the concept that varespladib might have a favorable effect on clinical event rates. In the $sPLA_2$ Inhibition to Decrease Enzyme Release after Percutaneous Coronary Intervention (SPIDER-PCI) study, 144 patients scheduled to undergo an elective, planned intervention were treated with either varespladib 500 mg or placebo twice daily, from 3 to 5 days before their procedure through to 5 days following successful intervention. Treatment with varespladib was associated with smaller postprocedural rises in $sPLA_2$ levels, suggesting a potential favorable effect in the setting of coronary revascularization [24].

The Phospholipase Levels and Serological Markers of Atherosclerosis (PLASMA) study evaluated the effect of treatment with varespladib 50–500 mg or placebo twice daily for 8 weeks in patients with stable coronary artery disease. Dose-dependent reductions in $sPLA_2$, associated with a 10% reduction in LDL-cholesterol, were observed with varespladib. The improvement in lipid profile was predominantly driven by a reduction in the concentration of small, dense LDL particles with the $sPLA_2$ inhibitor [25]. A follow-up study (PLASMA-2) confirmed LDL-cholesterol lowering with varespladib, when administered in statin-treated patients with established coronary artery disease, suggesting potential lipid-modifying effects in addition to its impact on inflammatory pathways [26].

These biomarker findings were subsequently investigated in patients with an acute coronary syndrome, treated with potent statin therapy. In the Fewer Recurrent Acute Coronary Events with Near-term Cardiovascular Inflammation Suppression (FRANCIS) study, patients within the first 96 hours of an acute coronary syndrome, with diabetes, metabolic syndrome or an elevated C-reactive protein (CRP) level, treated with atorvastatin 80 mg daily were treated with varespladib or placebo. A beneficial effect was observed in the varespladib group, with greater reductions in $sPLA_2$, LDL-cholesterol and CRP observed [27].

Each of these preliminary reports provided support for the concept that varespladib might have a favorable effect on cardiovascular event rates in patients at high vascular risk. The Vascular Inflammation Suppression to Treat Acute Coronary Syndrome for 16 Weeks (VISTA-16) study compared the effect of varespladib 500 mg or placebo daily for 16 weeks when administered to atorvastatin-treated patients, commenced within 96 hours of the acute event. Patients were required in addition to have: diabetes; metabolic syndrome; previous stroke or transient ischemic attack; peripheral vascular disease; or previous coronary revascularization [28]. In March 2012, the Data and Safety Monitoring Board recommended premature cessation of VISTA-16 due to futility [29]. The complete findings of the study have yet to be fully reported in the scientific literature, but will provide important information regarding the potential efficacy and safety of $sPLA_2$ inhibition in patients with coronary artery disease.

This has important implications not only for understanding the impact of varespladib on cardiovascular risk, but also for other phospholipase inhibitors. Darapladib, a pharmacological inhibitor of the lipoprotein-associated variant of the enzyme, is currently undergoing investigation in two large clinical outcome trials. Early studies suggest that daraplidib may have a favorable effect on the necrotic core of atherosclerotic plaques in patients with coronary disease [30]. Whether a similar finding of no clinical benefit as observed with varespladib will be reported is unknown.

Conclusion

Despite a large body of evidence implicating a role for $sPLA_2$ in the pathogenesis of atherosclerotic cardiovascular disease, the first pharmacological inhibitor to advance to a large clinical outcomes trial failed to show any cardiovascular benefit. Whether this reflects futility for the molecule itself or a broader failure for $sPLA_2$ inhibition in terms of cardioprotection remains uncertain. Nevertheless, the search to identify anti-inflammatory therapies to reduce cardiovascular risk continues. ■

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Heart Metab. (2013) 60:27-29

Trimetazidine effects on oxidative damage

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Abstract

Trimetazidine is an anti anginal medication and ensures the proper functioning of transmembrane ionic channels by maintaining intracellular ATP production in ischemic conditions. Trimetazidine prevents the accumulation of calcium in cardiomyocytes, adjusts cellular acidosis, and decreases production of free oxygen radicals. Trimetazidine blocks long chain 3-ketoacyl coenzyme A thiolase activity, thereby shifting ATP production more towards glucose oxidation instead of fatty acid β-oxidation during myocardial ischemia. By inhibiting fatty acid β-oxidation, fewer free radicals are formed in the cardiomyocytes with more efficient oxygen consumption and ATP production, resulting in recovery of myocardial contractile function and inhibition of malignant arrhythmias. Moreover, cardiac enzymatic activities such as phosphorylase and ATPase increased significantly in ischemic areas with trimetazidine pretreatment before myocardial ischemia. Protective effects of trimetazidine by increasing ventricular fibrillation threshold during coronary artery occlusion were consistent in animal studies. ■ Heart Metab; 2013;60:27–29

Keywords: Myocardial infarction; oxidative damage; trimetazidine.

Introduction

Trimetazidine is an anti-ischemic metabolic drug used for patients with angina pectoris [1], and trimetazidine increases myocardial glucose utilization by inhibiting fatty acid oxidation [1, 2]. Some studies have revealed that trimetazidine improves left ventricular contractile function in patients with heart failure, thereby improving NYHA functional class and left ventricular function [3, 4]. Trimetazidine has been known as a "metabolic agent" because it ensures the proper functioning of transmembrane ionic channels by maintaining intracellular ATP production in ischemic conditions. Trimetazidine inhibits long chain 3-ketoacyl coenzyme A (CoA) thiolase activity, thereby maintaining ATP production in ischemic cardiomyocytes [5]. By preventing fatty acid β-oxidation, the ba-lance between ATP demand and supply can be maintained in patients with ischemic heart disease. During the process of myocardial ischemia, reactive oxygen species (ROS) such as superoxide anion and hydroxyl radicals accumulate in ischemic cardiomyocytes, resulting in damage to mitochondria and ultimately leading to apoptotic cell death [6, 7].

Oxidative stress and myocardial ischemia

Cumulative oxidative stress could cause various diseases such as Alzheimer's disease, Parkinson's disease, and other neurodegenerative diseases [8]. Oxidative damage has been implicated in oxygen reperfusion injury following coronary ischemia. Large amount of ROS produced together with calcium overload after postischemic reperfusion damages mitochondrial membrane and increases its permeability [1, 2, 9]. Mitochondrial damage with ROS can lead to

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Abbreviations

ATP: Adenosine-5'-triphosphate; **CoA:** coenzyme; **ROS:** reactive oxygen species.

electrical instability with increasing chance of ventricular fibrillation. Antioxidants such as vitamins, superoxide dismutase plus catalase, and N-acetylcysteines have been used to reduce ROS burden after myocardial ischemia [10, 11]. Trimetazidine, acting as a potent antioxidant during myocardial ischemia, reduces ROS thereby stabilizing mitochondrial integrity. Properly functioning mitochondria, which are energy power plants in the cardiomyocytes, contribute in decreasing myocardial infarct size after ischemic injury, subsequently reducing the incidence of malignant ventricular arrhythmias (*Figure 1*).

During myocardial ischemia, ATP production shifts towards fatty acid oxidation over glucose oxidation [2, 12]. ATP generation shifting towards fatty acid oxidation during myocardial ischemia produces less energy with accumulation of lactate and proton responsible for acidosis [1, 13]. Increased fatty acid oxidation results in increased mitochondrial damage, resulting in decreased myocardial contractile function. Trimetazidine comes into play during myocardial ischemia by blocking long chain 3-ketoacyl CoA thiolase activity, thereby shifting ATP production more towards glucose oxidation instead of fatty acid β-oxidation [14]. By inhibiting fatty acid β-oxidation, fewer free radicals are formed in the cardiomyocytes with more efficient oxygen consumption and ATP production, resulting in the recovery of myocardial contractile function and inhibition of malignant arrhythmias. Trimetazidine not only inhibits fatty acid β-oxidation, but also increases glutathione peroxidase, which is known as an antioxidant enzyme [1]. Mitochondrial structure and function can be maintained by preventing fatty acid β-oxidation and ROS production, and the beneficial effects of trimetazidine translate into a decrease in myocardial infarct size of more than 20% [1, 2]. Moreover, during postischemia reperfusion after myocardial ischemia, fatty acids such as palmitate can damage the myocardial contractile function by inducing mitochondrial uncoupling [2]. Mitochondrial uncoupling not only decrease ATP production but also promotes the development of ROS during myocardial ischemia. Palmitate induces the production of ascorbyl free radicals during the reperfusion period with subsequent mitochondrial damage and free radical formation [2]; however, trimetazidine pretreatment was shown to prevent ascorbyl free radical release during the postischemic period in rat hearts [2]. The release of ascorbyl free radical was associated with the production of oxygen free radicals during postischemic reperfusion, and was negatively correlated with cardiac contractile function [2]. Trimetazidine at high concentration competes with cytochrome c in clearing superoxide radicals produced by xanthine oxidase [2].

Cardioprotective effects of trimetazidine

Trimetazidine prevents ischemic damage to cardiomyocytes by preserving mitochondrial structure and function, and the production of ROS has been re-

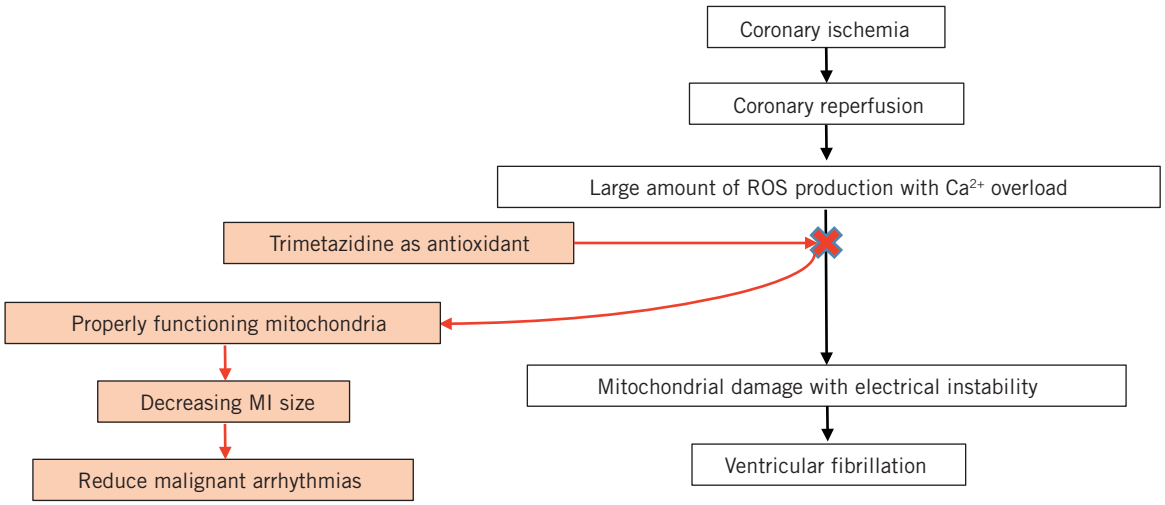

Fig. 1 *Trimetazidine reduces reperfusion myocardial injury by reducing mitochondrial damage. MI=myocardial infarction.*

duced by more than 30% with a 2-fold increase of oxidative phosphorylation [1]. In an experiment with swine, the effects of trimetazidine 20 mg immediate release and trimetazidine 35 mg modified release administered twice a day for four consecutive days were compared against placebo on ventricular fibrillation susceptibility during a 1-minute ischemia and on the protection of mitochondrial structure and function [1]. Ischemic areas were significantly reduced in pigs treated with trimetazidine, and mitochondrial structure and function were preserved after ischemic events in both trimetazidine-treated groups. The ventricular fibrillation threshold is lowered during myocardial ischemia, but trimetazidine increases the ventricular fibrillation threshold during ischemic conditions, thereby preventing malignant arrhythmia in ischemic heart disease [15, 16]. Trimetazidine prevents the accumulation of calcium in cardiomyocytes, adjusts cellular acidosis, and decreases the production of free oxygen radicals [1, 16]. Trimetazidine prevents ischemic ventricular fibrillation by maintaining homeostasis in cardiomyocytes. In trimetazidine-treated groups, cardiac enzymatic activities such as phosphorylase and ATPase increased significantly in ischemic areas in an animal experiment [1]. The protective effects of trimetazidine by increasing ventricular fibrillation threshold during coronary artery occlusion were consistent in both treated groups; however, no additional increase in the ventricular fibrillation threshold was found before occluding the coronary artery. Trimetazidine directly prevent cardiomyocyte vulnerability to ventricular fibrillation in ischemic conditions by balancing oxygen demand and supply [17].

Conclusion

Trimetazidine reduces oxidative damage after myocardial ischemia by reducing free radical oxidation products such as lipid peroxide and malondialdehyde in the mitochondria, thereby decreasing myocardial infarct size and ventricular fibrillation in animal studies. ■

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Psoriasis and risk of cardiovascular disease: case report and discussion

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Abstract

Psoriasis is a common inflammatory disease affecting 2% of the population. People who have severe psoriasis (requiring a systemic therapy) have a marked increase in cardiovascular disease. This could be due to an increased prevalence of traditional cardiovascular risk factors in people with psoriasis, the effect of chronic inflammation or a combination of both factors. Patients with severe disease should be risk assessed for cardiovascular disease and co-morbidities actively managed. ■ Heart Metab; 2013;60:30–33

Keywords: Psoriasis; inflammation; skin disease; cardiovascular disease; anti-TNF therapy.

Introduction

A 40-year-old lawyer has been followed in our severe psoriasis clinic since 2002. He first developed psoriasis in his twenties. He has a past medical history of mild psoriatic arthritis and hypercholesterolemia. He is an ex-smoker and drinks a moderate amount of alcohol. He is overweight (body mass index 26) but has no history of diabetes. He has a family history of ischemic heart disease. After 5 years of using topical skin treatments and phototherapy, in 2001 he required systemic therapy. He was treated with methotrexate, acitretin and cyclosporin between 2001 and 2007, when despite cyclosporin therapy, his psoriasis deteriorated.

The psoriasis area and severity index (PASI) is a validated and widely used disease severity scoring tool employed by the UK's National Institute of Health and Clincal Excellence (NICE) to guide suitability for systemic therapy. In 2007, his PASI score was 30.5 (range 0–72) and he therefore met NICE criteria for TNF antagonist therapy. He responded rapidly to 8-weekly infliximab infusions at 5 mg/kg (PASI 3 in March 2008) with complete disease control for 2 years. In August 2009 his psoriasis started to flare between treatments and his regime was altered to 6-weekly infusions.

In september 2009 he developed chest pain and shortness of breath during a trip to the hairdresser. He was hospitalized with an acute coronary syndrome, a troponin rise and an ischemic ECG. Slight chest pains during the infliximab infusion 7 days before the infarct triggered a collective decision to avoid further infusions, although the etiological relevance of infliximab in relation to the subsequent coronary event was never clear. Two months later his psoriasis flared. The initiation of bisoprolol and ramipril post infarction may have contributed to this; both drugs may exacerbate psoriasis [1]. During the same period he developed recurrent chest pain. In-stent restenosis was diagnosed and treated by a second angioplasty and stent within stent. A difficult year followed: his psoriasis was poorly controlled; stenoses in the RCA and left anterior descending arteries required stenting to alleviate chest pain and he also experienced two minor transient ischemic attacks. He underwent percutaneous coronary intervention of the RCA. Further episodes of chest pain in 2012 resulted in a coronary artery bypass grafting procedure.

In 2011, another systemic agent was sought to help control his severe psoriasis. Options were limited given his previous poor response to standard sys-

Abbreviations

CVD: cardiovascular disease; **ECG:** elctrocardiogram; **FAE:** fumeric acid esters; **IL:** interleukin; **JAMA:** Journal of the American Medical Association; **MACE:** major adverse cardiovascular event; **MI:** myocardial infarction; **RCA:** right coronary artery; **TNF:** tumour necrosis factor; **UK:** United Kingdom

temic therapy, and reluctance by both the patient and his cardiologist to try another TNF antagonist drug. He was therefore prescribed FAE, which induce apoptosis causing a reduction in peripheral CD4 and CD8 T cells and are used as first-line systemic therapy for chronic plaque psoriasis in Germany but remain unlicensed in the UK [2]. He achieved excellent disease control with FAE (PASI 2). In early 2013 this treatment was complicated by mild renal impairment with proteinuria presumed secondary to FAE therapy. A switch to ustekinumab, a monoclonal antibody (mAb) directed against the p40 unit shared by IL-12 and IL-23 (licensed for use in UK by NICE since 2009) for severe psoriasis is being considered but may be relatively contraindicated, in view of the possible link between p40 mAb (briakinumab, ustekinumab) and MACE [3].

Psoriasis

Psoriasis is a common inflammatory disease with environmental and genetic etiology, which affects approximately 2% of the population. The pathophysiology involves T-cell activation and release of cytokines including TNFα. Cutaneous inflammation combined with hyperproliferation of the epidermis results in erythematous, raised plaques with overlying scale. Nails are frequently involved and up to 30% of patients also have psoriatic arthritis [4, 5] (*Figure 1* [please note—the images used to illustrate this case are not of the patient described in the case report]).

Psoriasis and cardiovascular risk

A Swedish study published in 2004 attracted widespread interest when it reported that patients with psoriasis requiring hospital admission had a significantly increased risk of death from CVD compared to the general population [6]. This was followed by a large population-based study published in the JAMA, which identified psoriasis as a possible independent risk factor for MI [7]. A recent systematic review and meta-analysis designed to investigate incident CVD in people with psoriasis concluded that people who have severe disease (requiring systemic therapy or hospitalization) have a marked increase in CVD: the risk ratio relative to the general population for CVD mortality was 1.37 (95% CI 1.17–1.60) and 3.04 (95% CI 0.65–14.35) for MI. The relative risks of CVD were highest in the younger, severe disease population (3.10 [95% CI 1.98-4.86] for MI at 30 years) [8]. As a result of such research, psoriasis was cited as an independent risk factor for MI in the 2012 European guidelines on CVD prevention, which also recognize that the relative risk of MI is greatest in young patients and those with severe disease [5]. UK NICE guidelines published in October 2012 recommend that adults with severe psoriasis of any type should undergo a cardiovascular risk assessment at presentation using a validated risk assessment tool. They also recommend clinicians "offer a further assessment every 5 years or more frequently if indicated" [9].

The relationship between psoriasis and CVD is complex. Patients with psoriasis have an increased prevalence of coronary risk factors including metabolic syndrome [10, 11]. Psoriasis patients also tend to smoke more than the general population [12]. These factors may account for some if not all of the increased incidence of CVD seen in this group.

Inflammation has been recognized as an independent cardiovascular risk factor and there is an argument that a marker to reflect inflammation (such as highly sensitive C-reactive protein) should be added to cardiovascular risk scoring [13]. In an animal study using mice with psoriasiform dermatitis (KC-Tie2 mice) and an absence of comorbidities, aortic root inflammation was present in 33% of the affected KC-Tie2 group compared with 0% of controls (P = 0.04). After treatment of skin inflammation, the aortic root lesions resolved. The study showed that in murine models, skin inflammation alone promotes vascular inflammation and thrombosis [14]. The mechanisms linking psoriasis, metabolic syndrome and CVD have not yet been established in human subjects; one hypothesis invokes chronic T helper type 1 (Th1) inflammation [10]. A Th1-driven immune response that includes activated monocytes, macrophages and Th1 proinflammatory cytokines (including interferon and TNFα) is the hallmark of active psoriasis and also plays a role in metabolic syndrome and atherogenesis [4, 15].

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Anti-TNF therapy and CVD

If the relationship between psoriasis and CVD is causal – and currently this is not proved – then it can be hypothesized that treating psoriasis may abrogate the risk of CVD. With regard to older, oral systemic therapies for psoriasis (namely methotrexate, acitretin, cyclosporin), although it is accepted that certain drugs may increase individual cardiovascular risk factors (for example cyclosporin is linked to hypertension and dyslipidemia), the benefit of treating severe, active disease may decrease the overall incidence of MI [16–18].

Studies evaluating the effect of treatment with anti-TNFα therapies on the incidence of MI are ongoing. Published studies have shown mixed results; either lowering the risk or having no significant effect [18, 19]. There have been concerns that newer IL-12/23 agents (ustekinumab and briakinumab) may be associated with an increase in MACE. In 2011, after an elevated MACE rate was identified in a phase III briakinumab study, the sponsoring pharmaceutical company (Abbvie) withdrew the drug from further development. A JAMA meta-analysis [3] found no significant difference in the rate of MACE in patients with psoriasis treated with anti-TNFα/IL-12/23 agents compared to controls, although the study may have been underpowered and the authors advised clinicians to exercise caution in patients with identifiable cardiovascular risk factors when prescribing IL-12/23 agents. This year Papp et al [20] reviewed safety outcomes in patients treated with ustekinumab for up to 5 years and found no elevated risk of MACE. Although reassuring for clinicians, more comprehensive data from large, prospective registries are likely to give a clearer picture over the next 5–10 years.

Conclusion

Severe psoriasis is a risk factor for CVD. This could be due to an increased prevalence of traditional cardiovascular risk factors in people with psoriasis, the effect of chronic inflammation in patients with psoriasis or, more likely, a combination of both factors. Patients with severe disease should be risk-assessed for CVD and comorbidities should be actively managed. ■

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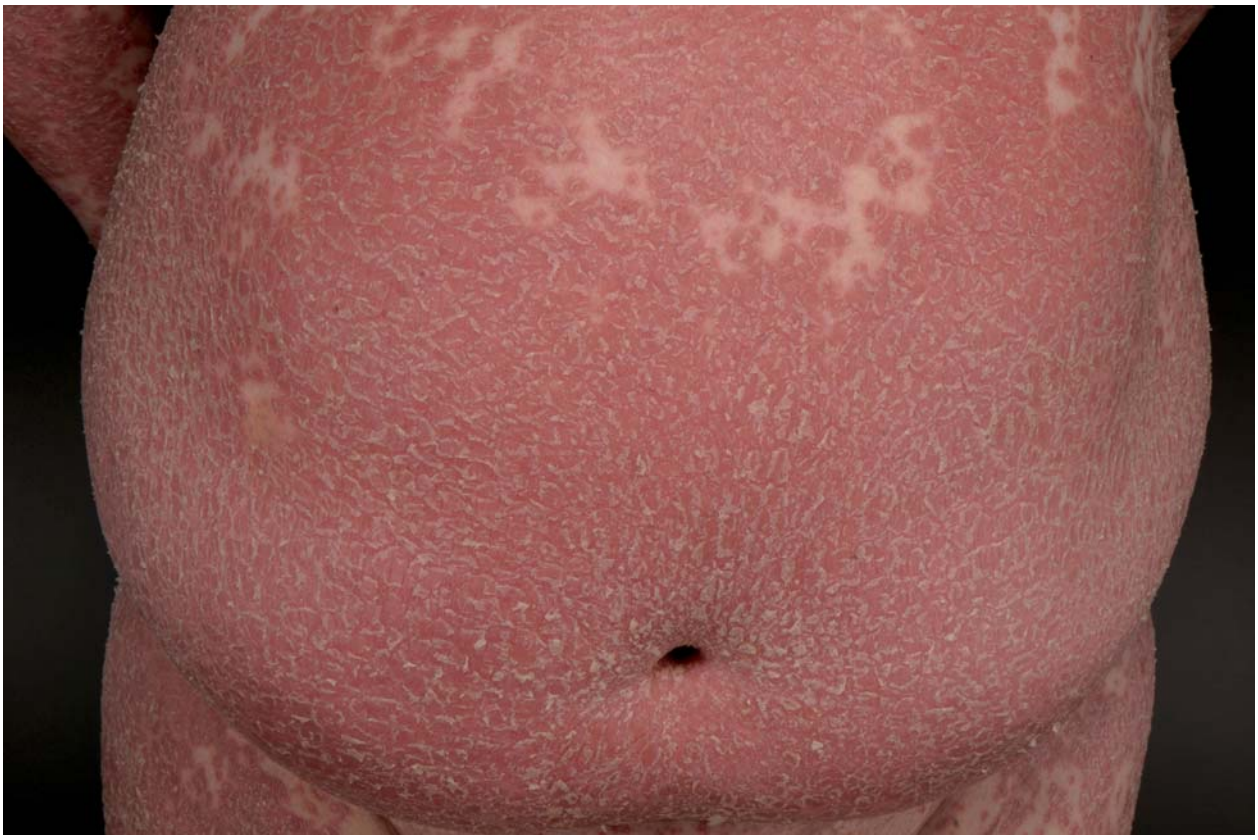

Fig. 1 *Patient with severe chronic plaque psoriasis.*

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Innate immunity: an integrated overview

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Abstract

The innate immune system with its multiplicity of molecular sensing mechanisms detecting numerous pathogen-derived and self-generated molecular patterns is now known to play a role not only in defence against invading microorganisms such as microbes, parasites, viruses and fungi, but also in promoting disease processes initiated by the release of endogenous danger molecules from damaged or inflamed cells. Causative roles have currently been established in the pathophysiology of cardiovascular disease, ischemic inflammatory injury, lymphocytic leukemia, asthma, rheumatoid arthritis, chronic obstructive pulmonary disease, malignant melanoma, acute pancreatitis, diabetes and even chronic pain. Major mediating mechanisms involve Toll-like receptors, NOD-like receptors, retinoic acid inducible gene receptors, cytosolic DNA receptors and C-type lectin receptors, often in combination. Therapeutically targeting one or more of these sensors or pathways could lead to novel approaches to the treatment of a wide range of common disorders and inflammatory diseases. ■ Heart Metab; 2013;60:34–37

Keywords: C-type lectin receptors; innate immunity; NOD-like receptors; RIG-1-like receptors; Toll-like receptors.

Introduction

Current understanding of regulatory mechanisms underlying innate immunity has increased markedly over the past two decades. No longer are these integrated pathways viewed simply as a first line of defence against invading pathogens, such as bacteria, viruses and fungi, but are now also recognized as important sentinels and mediators of intrinsic pathophysiological events involved in inflammation, autoimmunity and chronic disease [1–10].

Five major groups of highly conserved membrane-bound and soluble receptors (PRR) have so far been identified that can recognize a broad range of characteristic pathogen-specific molecules (PAMP) or endogenous danger molecules released from damaged or dying cells (danger associated molecular patterns, DAMP). These include TLR, NOD-like receptors (nucleotide-binding oligomerization domain receptors), retinoic acid inducible gene receptors (RIG-1-like receptors), cytosolic DNA receptors and CLR.

PRR activation leads to the initiation of downstream mechanisms aimed at pathogen destruction and elimination, or initiation of sterile inflammation and autoimmune disease. In this sense the innate immune response may be a double-edged sword that requires careful regulation in order to avoid extensive and progressive autoimmune damage. Mediator molecules include IL-1β and IL-18, which stimulate interferon-gamma (IFNγ) production and initiate the development of T helper type 1 responses. This further amplifies cytokine release and triggers pathogen removal. Other mechanisms include the induction of microbial peptides, pyroptotic (caspase-1-dependent) cell death, phagocyte recruitment and induction of autophagy [11].

ABBREVIATIONS

AIM: absent in melanoma-2; **ASC:** apoptosis-associated speck-like protein containing a CARD; **CARD:** caspase activation and recruitment domain; **CD14:** Cluster of differentiation 14, a co-receptor; **CLR:** c-type lectin receptors; **CpG DNA:** a DNA site, cytosine and guanine separated by one phosphate; **CRD:** conserved carbohydrate recognition domains; **DAI:** DNA-dependent activator of IFN-regulatory factors; **DAMP:** danger associated molecular patterns; **DC:** dendritic cells; **DC-SIGN:** Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; **DNGR-1:** DCNK lectin group receptor-1; **dsDNA:** double stranded DNA; **ICAM:** intercellular adhesion molecule; **IFN:** interferon; **IKK:** inhibitor of nuclear factor κ-B kinase; **IRF:** interferon regulatory factor; **LGP2:** Laboratory of Genetics and Physiology-2; **LRRFIP1:** IL-β Leucine-rich repeat flightless-interacting protein 1; **MHC:** major histocompatibility complex; **mincle:** macrophage inducible C type lectin; **NEMO:** NF-κ-B essential modulator; **NF-κ-B:** nuclear factor kappa-B; **NLR:** NOD-like receptors; **PAMP:** pathogen associated molecular patterns; **PRR:** pattern recognition receptors; **STING:** stimulator of IFN genes; **TLR:** Toll-like receptors **TNF:** tumor necrosis factor

Toll-like receptors

TLR were the first and are the most characterized of all PRR so far studied. All are homologues of the *Drosophila* Toll gene, first identified in 1985 as an important factor in embryogenesis, immunity to fungal infections and later in 1997 in mammals as Toll-related protein (TLR4). All TLR (10 in humans) are type 1 transmembrane proteins that share a common structure composing a single membrane-spanning region, an N-terminal extracellular leucine-rich domain and a C-terminal cytoplasmic tail containing a conserved region known as the Toll/IL-1 receptor domain. Receptors have their own individual specificity and often recognize several PAMP. TLR2 is essential for the recognition of a broad range of PAMP, including bacterial lipoproteins, peptidoglycan and lipoteichoic acids, whereas others may be more specific. TLR3 is implicated in virus-derived double stranded RNA recognition. TLR4 is predominantly activated by lipopolysaccharide. TLR5 detects bacterial flagellin while TLR9 is required for response to unmethylated CpG DNA. TLR7 and TLR8 have recently also been shown to recognize small synthetic antiviral molecules. In many instances, TLR require the presence of a coreceptor to initiate the signaling cascade. TLR4, for example, interacts with MD2 and CD14, a protein that exists both in soluble form and as a glycophosphatidylinositol-anchored protein, to induce nuclear factor κB (NFκB) in response to lipopolysaccharide stimulation.

NOD-like receptors

NLR are intracellular cytoplasmic sensors that recognize a wide variety of PAMP, which enter the cell via phagocytosis or pores, as well as endogenous DAMP released in response to cell stress or damage. NLR are found throughout the animal kingdom in lymphocytes, macrophages and DC as well as some non immune cells, for example epithelium.

Activation of NLR proteins, NLRP3, NLRP1 and NLRC4 and the interferon inductible 200 family member absent in melanoma-2 (AIM2) results in the formation of large protein complexes termed inflammasomes. Once activated NLRP3, NLRP1, NLRC4 and AIM2 undergo a conformational change that allows interaction with an inflammasome-adaptor protein, ASC (PYCARD), which, in turn, interacts with caspase-1. The resulting inflammasome facilitates the autoactivation of caspase-1, which cleaves the pro-forms of IL-1β and IL-18 to active forms. Inflammasome activation is crucial for host defence to pathogens, but recent research has also identified a role in the pathogenesis of several inflammatory diseases such as type 2 diabetes, inflammatory bowel disease and atherosclerosis [12].

C-type lectin family

Soluble C-type (calcium-dependent) and membrane-bound lectin receptors (CLR) are a large family of antifungal innate immunity receptors that recognize a wide range of carbohydrates on pathogen surfaces. Type 1 receptors include DEC-205 and the macrophage mannose receptor, which contain several CRD and are transmembrane proteins. Type 2 receptors in contrast typically carry a single CRD and include Dectin-1, Dectin-2, mincle the DC-specific ICAM3-binding non integrin and DNGR-1, which are important in viral recognition, DC trafficking and the formation of the immunological synapse. Mannose-binding lectin is a soluble CLR that may play important roles in transplant rejection, cardiovascular disease and other secondary consequences of diabetes [13, 14]. CLR activation triggers key signaling path-

ways that induce the expression of specific cytokines or directly activate NFκB, thereby modulating signaling by TLR or triggering complement activation via the lectin pathway *(Figure 1)*. Therapeutically, CLR signaling may have important significance in the development of innovative approaches to vaccine development. Targeting specific CLR may be a powerful method to enhance antigenicity and influence whether antigen is presented in the context of MHC class I or MHC class II molecules. MHC class I presentation is vital for inducing strong CD8 T-cell responses, necessary for immunity to HIV-1. DNGR-1 may have particular significance because of its restricted pattern of expression to DC that may be exploited in cancer therapy [15].

RIG-1-like receptors

RNA helicase RIG-1 receptors (RIG-like receptors, RLR) are proteins that in general specifically recognize viral RNA and act as sensors of viral replication within the cytoplasm of human cells. They include the cytosolic RNA sensors RIG-1, MDA5 and LGP2 (encoded by the gene DHX58 and termed Laboratory of Genetics and Physiology 2). RIG-1 and MDA5 possess the ability to induce a cellular response via a so-called N-terminal caspase recruitment domain (CARD domain) when viral dsRNA is detected. Whereas LGP2, the remaining RLR, lacks the ability to induce signaling on its own (due to the absence of a CARD domain), it has recently been shown to be a potential coreceptor necessary for effective RIG-1 and MDA5-medi-

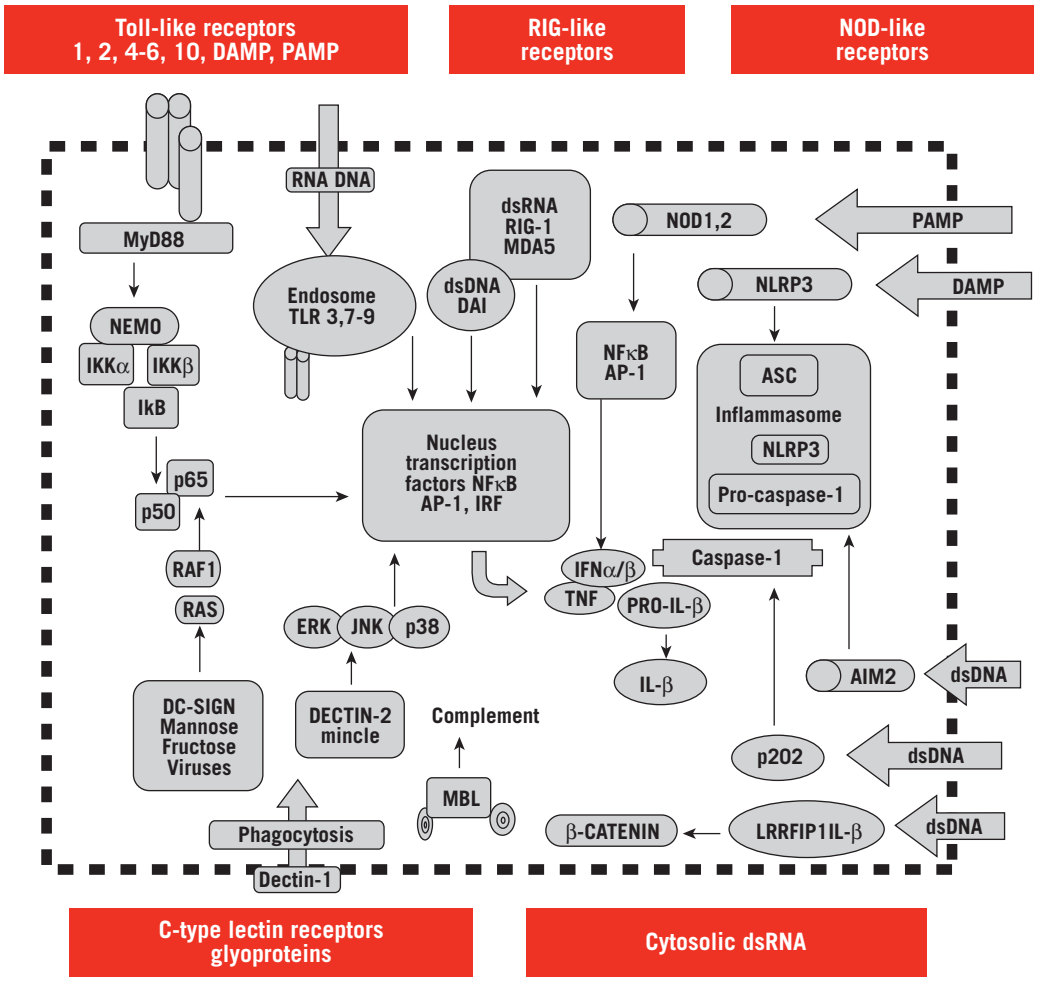

Fig. 1 *Schematic overview of the major molecular pattern-sensing mechanisms and downstream signaling cascades of the innate immune system. AIM2, absent in melanoma-2; AP-1, activator protein 1; ASC, apotopsis-associated speck-like protein containing a CARD; DAI, DNA-dependent activator of IFN-regulatory factors; DAMP, danger associated molecular pattern; DC-SIGN, DC-specific ICAM3-binding non integrin; ERK, extracellular signal-related kinase; IFN, interferon; Ik, inhibitor of nuclear factor κ; IKK, inhibitor of nuclear factor κ kinase; IRF, interferon regulatory factor; JNK, c-jun N-terminal kinase; LRRFIP, leucine-rich repeat flightless-interacting protein; MBL, mannose-binding lectin; NEMO, NFκB essential modulator; NFκB, nuclear factor κB; NOD-like receptor, nucleotide-binding oligomerization domain receptor; PAMP, pathogen associated molecular pattern; RIG-like receptor, retinoic acid inducible gene receptor; TLR, Toll-like receptor; TNF, tumor necrosis factor.*

ated antiviral responses to certain ligands. Abberant RLR signaling or dysregulated RLR expression has been implicated in the development of autoimmune diseases, therefore RLR-targeted therapeutics may be useful for antiviral and immune-modifying applications [16].

Cytosolic dsDNA sensors

While the recognition of extracellular DNA involves mainly TLR9, recognition of cytosolic DNA involves a complex array of sensors including DNA-dependent activator of IFN-regulatory factors (DAI) and leucine-rich repeat flightless-interacting protein (LRRFIP1), encoded by the *LRRFIP1* gene that trigger different signaling pathways in a cell-specific manner.

The first identified cytosolic DNA sensor, termed DAI, binds cytosolic dsDNA and leads to the production of type I interferon. Furthermore, the DNA sensor IFI16 (gamma-interferon-inducible protein I), part of a larger protein family termed the pyrin and HIN domain (PYHIN) family, has been found to recruit STING, an endoplasmic-resident transmembrane protein induced by an IFN-inducible ligase, to activate a TANK-binding kinase/interferon regulatory factor-dependent pathway to IFN-β induction.

Another member of the PYHIN family, AIM2, is a cytosolic DNA receptor that forms an inflammasome with ASC, a common adapter of inflammasomes, leading to caspase-1 cleavage and secretion of IL-1β and IL-18. p202 is yet another member of the PYHIN family that binds cytoplasmic dsDNA but, in contrast to AIM2, represses caspase activation *(Figure 1)*.

On the other hand, the cytosolic nucleic acid-binding protein LRRFIP1, on binding dsDNA triggers the production of IFN-β in a β-catenin-dependent manner. β-Catenin binds to the C-terminal domain of IRF3 inducing an increase in IFN-β expression. More recently, the helicase DDX41 has been identified as an additional DNA sensor that depends on STING to sense pathogenic DNA. Therefore, the recognition of cytosolic DNA is considerably more complicated than first anticipated. Clearly, several sensors have been identified that trigger different cell-specific signaling pathways. The general consensus, however, is that yet another unknown cytosolic DNA recognition system may exist. Additional studies to elucidate the complex mechanisms of cytosolic DNA recognition may facilitate the development of new strategies to treat inflammatory diseases [16–18]. ■

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Can infective agents be respectable etiopathogenetic factors for acute coronary syndromes?

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A policeman sees a drunk man searching for something under a streetlight and asks what the drunk has lost. He says he lost his keys and they both look under the streetlight together. After a few minutes the policeman asks if he is sure he lost them here, and the drunk replies, no, that he lost them in the park. The policeman asks why he is searching here, and the drunk replies "this is where the light is".

Atherosclerosis is a multifactorial disease and, among others, inflammation and activation of immune system play well established roles [1, 2]. In ACS, epicardial thrombosis with abrupt vessel occlusion is a crucial final event, initiated at the site of a "vulnerable plaque" [3]. Until recently, plaque rupture was considered predominantly mechanical, occurring at sites of vessel narrowing with turbulent blood flow [4]. However, removal of coronary stenosis has never proved to prevent ACS. On the other hand, exacerbation of inflammatory [5] and specific immune mechanisms has been implicated in platelet function modulation and thrombus formation in ACS [6, 7]. Therefore, pathophysiological pathways underlying the dynamic changes that ultimately cause coronary thrombotic occlusion represent an area of intense interest and research.

Inflammatory response in ACS includes systemic immune activation, local inflammation of the atherosclerotic plaque and immune reactions associated with the thrombotic event itself [8, 9]. Given the profound involvement of immune activation in ACS, infections and other systemic inflammatory reactions have also been proposed to increase the risk of ACS. Indeed, up to 30% of myocardial infarctions occur after upper respiratory tract infections [10], and chronic infectious agents such as *Chlamydia pneumoniae* or oral pathogens, initially linked to atherosclerosis, have been found to increase the risk of ACS [11–13]. In a very recent issue of *Circulation*, Pessi et al [14] assessed bacterial DNA in thrombus aspirates of 101 patients with STEMI and sought to determine the association between bacterial findings and oral pathology. They used real-time quantitative polymerase chain reaction with specific primers and probes to detect bacterial DNA from several oral species and *C. pneumoniae*. Bacterial DNA typical of endodontic infection was identified in 78.2% of thrombi, and periodontal pathogens were measured in 34.7%. In addition, bacteria-like structures (including whole bacteria) and monocyte/macrophage markers for bacteria recognition and inflammation were detected by transmission electron microscopy and immunohistochemistry analysis, respectively. In a subgroup of 30 STEMI patients examined with panoramic tomography, there was a significant association between periapical abscesses and oral viridans streptococci DNA-positive thrombi. The authors concluded that dental infection and oral bacteria, especially viridans streptococci, may be associated with the development of acute coronary thrombosis.

Such results are in line with another recent study, which also showed a lack of association between the severity of coronary atherosclerosis and periodontal

ABBREVIATIONS

ACS: acute coronary syndrome; **STEMI:** ST-segment elevation myocardial infarction

bacteria [15]. A number of mechanisms that explain an infective etiology of atherosclerosis and ACS, including direct effects on vascular cells, circulating cytokines and inflammatory mediators, as well as initiation of autoimmune reactions have been proposed [16]. Returning to the above-mentioned study, the presence of bacterial DNA together with co-stimulation of immune-specific cells in the thrombus aspirates may suggest that these pathogens disseminate into systemic circulation, migrate to coronary plaques, and cause and/or maintain inflammation of the coronary artery [17].

At present the role of infective agents in ACS is not completely understood. Nonetheless, antimicrobial therapies have already been tested in ACS prevention trials [18–20]. Although treatment results have been contrasting, the objective evidence of bacterial particles in the coronary thrombi should further enhance research in this direction. Indeed, while technological progress has permitted continuous improvement in coronary artery plaque and thrombus removal, this should not prevent us from exploring other, maybe less evident, but probably as relevant causes of ACS. ■

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Autoimmunity

Autoimmunity is a pathological process characterized by immune system activation (innate and adaptive) against self (ie, non foreign) antigens that ultimately leads to tissue inflammation and damage.

C-reactive protein (CRP)

CRP is a plasma protein produced by the liver. CRP is a member of the class of acute phase reactants, and its levels rise when inflammatory processes occur in the body. CRP assists in complement binding to foreign and damaged cells and enhances phagocytosis by macrophages. It therefore plays an important role in immunity and defence against infections. Because CRP rises dramatically during inflammation, measurement of its level in the blood can be used as a marker of inflammation.

Dendritic cells

Dendritic cells are antigen-presenting cells that link the innate (ie, nonspecific) and adaptive (ie, specific) immune systems. Dendritic cells are important in initiating T-cell activation and responses.

Inflammasome

The inflammasome represents large intracellular protein complexes/platforms participating in the innate immune response that mediate the activation and recruitment of inflammatory cells to the affected site in the body by the release of proinflammatory mediators.

Inflammation

Inflammation is the normal response to stimuli including physical (eg, physical injury) and chemical stresses (eg, foreign substances in the body) that elicit cellular damage. The inflammatory process is characterized by distinct phases including initiation, the recruitment of cellular mediators and the release of inflammatory mediators, and contributes to tissue repair following injury. An inappropriate and/or prolonged inflammatory response that is not self-limiting can contribute to cellular damage.

M1 macrophages

Macrophages are cells that arise from differentiated monocytes that have migrated into tissue. They are phagocytes that have a function in both innate and adaptive immunity. As macrophages are technically phagocytes, they play a primary role in phagocytosing cellular debris and pathogens. The M1 macrophage refers to the classically activated macrophages that act as immune effector cells and are traditionally proinflammatory (ie, they produce and release a number of proinflammatory cytokines), and are activated in response to endotoxins such as lipopolysaccharide.

M2 macrophages

The M2 macrophage in general is a term to describe a macrophage that is not the classically activated M1 macrophage (ie. alternatively activated macrophage), often referring to those macrophages that are involved in wound healing and tissue repair. M2 macrophages are able to tone down immune system responses by the production of anti-inflammatory cytokines such as IL-10 and IL-13.

Oxidative stress

Oxidative stress in general is the deterioration in normal redox state primarily caused by an imbalance between pro-oxidants and anti-oxidants sufficient to induce modification/damage of macromolecules. This results in the production of peroxides and free radicals that are often toxic to cells by damaging DNA, lipids, and proteins.

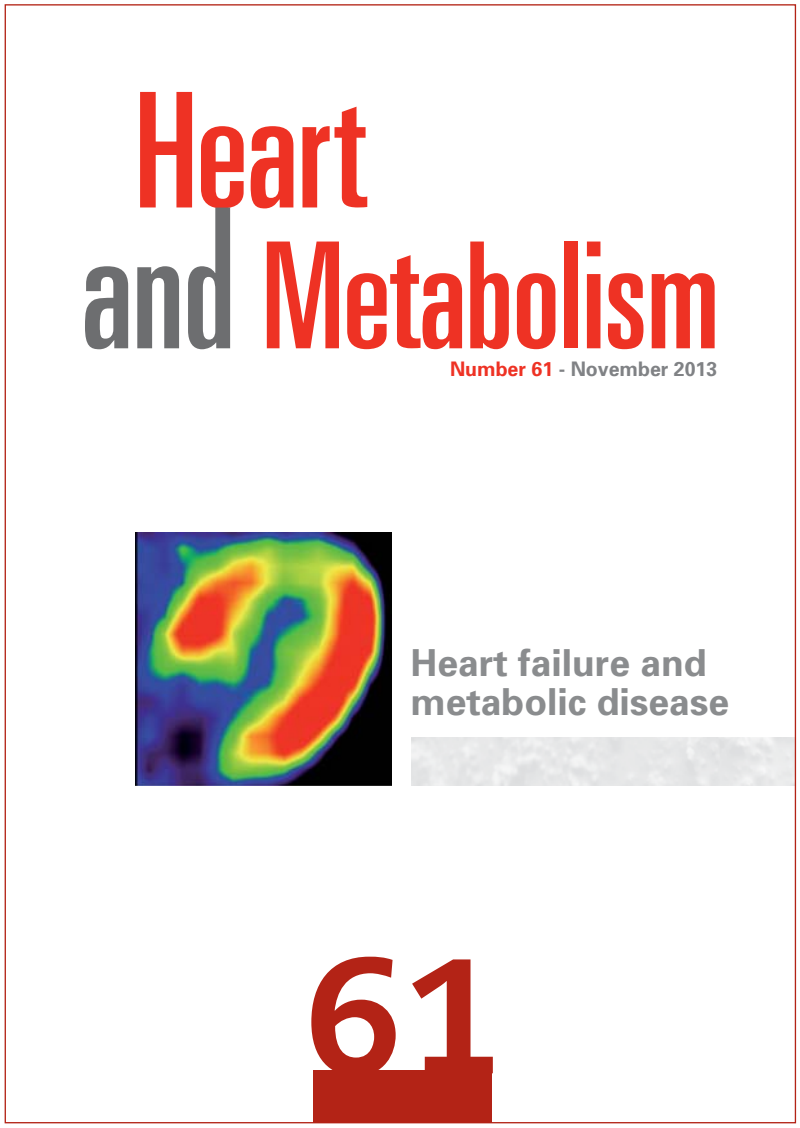
Proteinuria

Proteinuria refers to the excess presence of serum proteins (eg, albumin) in the urine, and typically occurs following glomerular lesions.

Secretory phospholipase A_2 ($sPLA_2$)

The phospholipase A_2 family of enzymes specifically release fatty acids from the second carbon group of glycerol by hydrolysis of the sn-2 ester bond of phospholipids in cell membranes and circulating lipoproteins, resulting in the generation of arachidonic acid and lysophospholipids. $sPLA_2$ is the secreted, extracellular form of the enzyme, and has been shown to promote inflammation in the vasculature and to correlate positively with the incidence of coronary artery disease. $sPLA_2$ inhibition has thus been pursued as a target for the reduction of cardiovascular risk.

In the next issue:
Heart failure and metabolic disease



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