The struggles of translational medicine in ischemia-reperfusion injury

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The almost 50 years of research on ischemia-reperfusion (IR) injury have been rewarded by the discovery of numerous pathways that have permitted a better understanding of the phenomenon. In fact, it is now universally accepted that IR is the result of precisely orchestrated biological events, ultimately resulting in additional harm to the ischemic myocardium. However, as is the case in other research areas, modulation of the individual "player" often does not result in expected benefits. Given the enormous research efforts in this area, such an aspect is becoming increasingly worrisome and deserves some critical appraisal.

When findings are transferred from bench to bedside there are 3 main levels where failure may take potential origin: a) applying molecular findings to biological systems, b) applying animal model findings to humans, and c) applying the findings in the wrong timing.

Applying molecular findings to biological systems

Intracellular transduction pathways form a fit net of network that may interact at different levels so that, modulation of a single pathway can be compensated to a variable degree by activation of alternative pathways. Alternatively, some signal transduction systems may share common initial pathways that do not necessarily result in the same final target.

For example, intracellular calcium overload, is a key intracellular event for IR injury [1]. Inhibition of L-type calcium channels [2], which regulate intracellular accumulation of calcium, has proven to benefit recovery from IR injury. However, not all L-type calcium channels blockers exert beneficial effects on infarct size. In fact, while verapamil has extensively been shown to reduce infarct size [2], nicardipine, another calcium antagonist that similar to verapamil inhibits L-type calcium channels, has not been shown to induce similar benefits [3].

Applying animal-model findings to humans

There are several factors to be considered when experimental findings are transferred from experimental models to humans. First of all, the infarction model in experimental settings, constituted from artery ligation, is profoundly different from the "naturally occurring" myocardial infarction (MI). In fact, the latter occurs secondary to thrombotic occlusion and encompasses the three components of Virchow's model for thrombosis (vascular, hemodynamic and coagulatory), which themselves may alter the response to treatment. The "naturally occurring" MI can also be preceded by angina, a recognized natural preconditioning mechanism, thereby biasing the results of a given treatment among patients with or without pre-infarct angina. In addition, pre-infarct events can be important stimuli for development/activation of collateral vessels in human models. On the other hand, collateralization in animal models is significantly different (i.e., pig models are known to not develop collateral vessels) and can subsequently affect the results among different species.

Importantly, patients experiencing MI, may also be carriers of cardiomyopathies (i.e., myocardial hypertrophy) or other comorbidities (diabetes, hypertension, etc.) that can negatively affect the expected benefit of a given treatment. This is obviously not the case in animal models, where one is able to control for all these factors and produce a "purely experimental" MI.

Pharmacodynamic and pharmacokinetic differences between humans and other species should also be considered. For example, different pharmacodynamic and pharmacokinetic properties among different species have been described for cyclosporine, and are considered to be the basis for the inconsistent results among clinical trials [4] and animal models [5].

Outcome measures may as well significantly differ among different settings. In fact, human studies have measured outcomes based principally on the rise in myocardial enzymes [6]. On the other hand, experimental models have traditionally used histopathological analysis as outcome measure.

Another practical issue is that, while easily performed in experimental models, delivery of cardioprotective agents before MI onset is difficult to achieve in clinical practice.

Applying the findings in the wrong timing

Following an acute MI, early and successful flow restoration is the most effective strategy to reduce infarct size and improve outcome [7]. Importantly, while progressively decreasing in magnitude thereafter, the largest achievable benefit is concentrated in the first 2–3 hrs after symptom onset [8].

Reperfusion injury is closely related to the preceding ischemic injury. In particular, the two phenomena display a peculiar time-dependent relationship. Myocytes experiencing an ischemic time that is long enough to cause irreversible damage will not benefit from restoration of blood flow, and hence, protection from IR injury. On the other hand, reperfusion therapy may benefit the myocardium presenting in the time window in which cells are still viable (salvageable myocardium) [9]. However, it is exactly at this stage that reperfusion can turn out to be the cause of relevant additional harm, so that, the greater the salvageable myocardium, the greater the potential harm from reperfusion [10], but also the benefits that can be observed from targeted therapy. It is also important to note that different cells (i.e., endothelial, inflammatory and myocardial) display different time-related response to ischemia. For instance, following reperfusion, the microcirculation undergoes a profound degree of endothelial dysfunction within minutes (i.e., 2.5 to 5 min) [11].

Conclusions

A consistent part of the enthusiasm achieved from research in IR injury gets lost in translation when findings are applied into the clinical setting. For this reason, research efforts should be centered to treatment agents that have been shown to have a reliable cause-effect property, to be reproducibly effective in experimental models, and ultimately, to test the specific hypotheses in carefully designed clinical trials. Besides the proper selection of the optimal treatment, the design of an effective strategy to prevent IR injury must also consider the timing and the site of the intervention that is, using the right agent at the right spot! •

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