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EDITORIAL COMMENT

There's more to a coronary thrombus than just platelets and fibrin – a new potential therapeutic target in the form of SGK-1 modulation?

Há mais num trombo coronário que apenas plaquetas e fibrina – haverá um novo alvo terapêutico potencial na modulação da SGK-1?

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The fundamental role of medical therapy in reducing the risk of cardiovascular events, particularly acute coronary syndromes (ACS), has been clearly established. The development of powerful anti-thrombotic and lipid-lowering agents, together with the treatment and prevention of other cardiovascular risk factors, has led to a significant improvement in the morbidity and mortality of cardiovascular disease in recent decades.[1]

Epidemiological studies have provided unequivocal data that clearly highlight these accomplishments. For example, the 30-day mortality rate of ACS in Sweden has dropped from over 15% in 1995 to just over 5% in recent years.[2] In Portugal, ACS in-hospital mortality has decreased by nearly 2/3 in this century alone, with the increased use of reperfusion strategies and pharmacotherapy.[3] Concomitantly, the relative proportion of non-ST elevation myocardial infarction vs. ST elevation myocardial infarction (STEMI) has been increasing[2] – hence, ACS is not only becoming less lethal, but also less severe and extensive.

Clinical trials have also very clearly showcased such trends. In the pivotal 4S trial published in 1994, the first major randomized trial with a statin, the one-year myocardial infarction rate was higher than 10%,[4] an inconceivable event rate in today's trials of atherosclerotic disease. Indeed, in the recent landmark trial ISCHEMIA, the power of intensive combined medical therapy was made very clear, as investigators were forced to widen the primary endpoint definition, including less ''hard'' events, due to lower than expected event rates[5] – a common issue when designing and conducting trials nowadays. One might say we are happily becoming victims of our own success.

Despite these substantial achievements, the need for further improvements in the therapy and prevention of ACS remains relevant. While the paradigm of mortality has been changing in the developed world, with the relative weight of cardiovascular disease falling in favor of cancer, the former remains the major cause of morbidity and mortality.[1] Thus, developing new therapeutic strategies should continue to be a major concern for the scientific community. Basic and translational science are an essential tool in the process.

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Indeed, only by ''going back to the basics'' can one reappreciate the biocellular pathophysiological pathways, which may be potential new targets for pharmacotherapy agents. The study by Cai et al.,[6] published in this edition of the Portuguese Journal of Cardiology, aimed to do just that.

The authors sought to explore the differences in coronary blood protein expression between patients who underwent primary percutaneous intervention due to STEMI, compared with a control group with normal coronary angiograms and no prior myocardial infarction (MI), but a significant burden of cardiovascular risk factors, including hypertension (53.3%) and smoking habits (20.0%). To do so, aspirated coronary blood with thrombus from the STEMI group was compared with coronary blood of the control group. The authors went on to find a number of significant differences between the two protein profiles, the most notable of which was the expression of serum-glucocorticoid-regulated Kinase-1 (SGK-1), which was expressed almost twice as much in the STEMI group, particularly in platelets.

SGK-1 is a serine/threonine-protein kinase involved in cellular stress response.[7] Some studies have suggested that it may be involved in regulating several aspects of platelet function.[8] As a result, the authors suggest that SGK-1 may be a key player in the pathophysiology of coronary thrombus formation, thus providing a potential therapeutic target in the treatment and/or prevention of ACS.

Available evidence suggests the role of SGK-1 is rather broad, albeit not yet entirely defined. From a clinical, and in particular cardiovascular perspective, it is worth pointing out that some studies do imply it may also play an important role in the development of hypertension[7] and diabetes,[9] as well as their target organ damage. The idea of inhibiting this protein with bespoke pharmacological agents has been put forward, especially for diabetes.[9] Paradoxically, animal studies have also hinted that SGK-1 activity may be relevant for increasing angiogenesis, as well as reducing cell death and infarct size after an MI.[10] Therefore, targeting this protein may be a double-edged sword.

Nevertheless, if Cai et al.[6] are correct in their hypothesis and SGK-1 does indeed play a direct role in the pathophysiology of STEMI, by enhancing and promoting thrombus formation, exploring it as a potential therapeutic target would be a path certainly worth considering. It may have a significant impact on a multitude of mechanisms, by both influencing the pathophysiology of ACS directly, but also the development of atherosclerotic disease as a whole by interacting with key risk factors, in particular diabetes and hypertension.

The study by Cai et al.,[6] is of course not without its limitations, which are acknowledged by the authors. In addition to the small sample size and single-center data, perhaps the most important aspect is the heterogeneity of the control and experimental groups. While some differences would be expected, given the clinical context, the control group has a much lower prevalence of diabetes than the STEMI group (10.0% vs. 46.7%). Given the reasonably documented increased expression of SGK-1 in patients with diabetes, one cannot be sure that the differences between groups were not primarily a consequence of this, rather than the occurrence of an MI per se. However, the fact that this has not been previously clearly documented in thrombus tissue (especially from human coronary arteries) renders the authors' hypothesis plausible, while adding a novelty factor as well.

Despite the limitations of the study, the authors deserve to be congratulated. Following a thorough review process, they have produced an interesting and thought-provoking paper. As those who are involved in original research are keenly aware of, conducting translational studies, especially in humans, is a challenging endeavor. The work by Cai et al.[6] should not be viewed as a landmark finding for now, but rather a novel hypothesis generating study. The path to scientific progress is more often made of small steps from multiple groups, rather than major sudden leaps by a single person or cluster. Time will tell whether the modulation of SGK-1 proves to be an important therapeutic target. Whether Cai et al.[6] are proven right or not, their nonetheless relevant contribution has been made public in this edition of the Portuguese Journal of Cardiology.

Conflicts of interest

The author has no conflicts of interest to declare.

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