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EDITORIAL

HSP90 inhibitors as a future therapeutic strategy in diabetes-driven atherosclerosis☆

Inhibidores de HSP90 como futura estrategia terapéutica en la aterosclerosis asociada a diabetes

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The presence of diabetes significantly increases the risk of atherosclerosis and associated cardiovascular diseases, thus making cardiovascular disease the leading cause of morbidity and mortality in people diagnosed with type 1 (DM1) and type 2 (DM2) diabetes mellitus. Currently, atherosclerosis is considered a chronic inflammatory disease in which innate and adaptive immune responses are activated. In addition, this inflammation promotes oxidative stress, which in turn exacerbates the inflammation, thereby generating a vicious circle that causes atherosclerosis to develop. Therefore, attempting to attenuate both the inflammation and the oxidative stress may be a very effective therapeutic strategy for preventing or treating cardiovascular disease. In this context, HSP90 (*Heat shock protein 90*) is currently being studied as a therapeutic target for treating atherosclerosis. The role of this protein goes beyond its participation in the response to heat shock, since, owing to its role as chaperone, it takes part in many cellular processes. For example, HSP90 stimulates the inflammatory process through its ability to activate the transcription factor NF-κB (*Nuclear factor κB*). Once activated, NF-κB induces the transcription of inflammatory and pro-oxidant genes. In addition, NF-κB may affect oxidative stress thanks to its ability to inhibit Nrf2 (*Nuclear factor erythroid-derived 2-like 2*). This transcription factor is one of the most important mechanisms available for cells to fight oxidative stress, as it regulates the expression of genes which encode not only proteins involved in detoxification and elimination of oxidising agents, but also others responsible for maintaining the cells' antioxidant capacities.[1]

Lázaro et al. evaluated whether HSP90 inhibition was able to attenuate diabetes-associated atherosclerosis and whether this treatment increased the antioxidant capacity in atherosclerotic lesions through Nrf2 activation. In this study, the authors experimented on apoE-deficient mice, which were given streptozotocin (a toxin that destroys the beta cells of the pancreas) to induce DM1. They therefore obtained an animal model that showed a combination of hyperlipidaemia and hyperglycaemia. Although the treatment of these animals with the HSP90 inhibitor modified neither glycaemia nor the lipid profile, a considerable reduction in the size of the atherosclerotic lesions was observed. The HSP90 inhibition also caused an increase in Nrf2 activation in the atherosclerotic lesions that the authors presented by using an innovative technique developed in their laboratory to detect *in situ* the activation of transcription factors. This increase in Nrf2 activity in the aortic tissue was observed mainly in macrophages and smooth muscle

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cells, and it was accompanied by an increase in the expression of Nrf2-regulated antioxidant genes. The results of this study also indicate that HSP90 may induce autophagy, *i.e.* a process that degrades and recycles cellular components, the reduction of which seems to be implicated in various pathologies, including cardiovascular diseases.[2]

The results of this preclinical study are encouraging and reinforce the possibility that HSP90 inhibitors, due to their anti-inflammatory and antioxidant effects, may become a therapeutic option for treating diabetes-associated atherosclerosis. The beneficial effects derived from HSP90 inhibition could also be due to an increase in autophagy, although, as the authors stated, this possibility needs to be confirmed in new studies. The main finding of this study is the confirmation that HSP90 inhibition increases Nrf2 activation, which involves the enhanced antioxidant capacity of cells. This aspect may be beneficial in preventing or treating atherosclerosis, but it is difficult to establish which proportion of the anti-atherosclerotic effect is due to Nrf2 activation and which part is a consequence of the anti-inflammatory effect. Considering the close relationship between inflammation and oxidative stress, the inhibition of both processes is likely to cause a synergistic effect.

Inhibiting HSP90 may be useful for more than just preventing or treating atherosclerosis, because it has been shown to be effective in treating other conditions such as Alzheimer's disease.[3] However, one problem arising from this pharmacological strategy is that HSP90 is a critical regulator in many cell processes, and therefore, *a priori*, it is difficult to know whether inhibiting this protein will cause adverse effects.[3] For this reason, new HSP90-inhibitor compounds specific for certain isoforms of this protein or drugs that specifically block some of the many complexes that HSP90 forms with other co-chaperones are now being developed.

In conclusion, this paper represents a significant advance in the study of the role that HSP90 inhibitors may play in the treatment of diabetes-associated atherosclerosis, and shows that reducing inflammation and enhancing antioxidant capacity is an effective strategy for attenuating atherosclerosis in animal models.

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