MARTÍN DONATO MTSAC

Gene Therapy to Treat Myocardial Infarction

Fattah C, Nather K, McCarroll CS, Hortigon-Vinagre MP, Zamora V, Flores-Munoz M. Gene therapy with Angiotensin-(1-9) preserves left ventricular systolic function after myocardial infarction. **J Am Coll Cardiol 2016;68:2652-66. http://doi.org/bwdz**

The renin-angiotensin-aldosterone system (RAAS) is involved in the control of cardiac function and hydroelectrolytic balance. This system was first described in 1889 by Tigerstedt, who defined renin as "a pressure substance isolated from the rabbit kidney". In 1934, Harry Goldblatt observed that constriction of the renal artery in one kidney was sufficient to induce a rise in blood pressure in dogs. In 1939, the Argentine group led by Bernardo Houssay, including Juan Carlos Fasciolo, Juan Mauricio Muñoz, Alberto C. Taquini, Eduardo Braun Menéndez, and Luis Federico Leloir, proposed the hypothesis of a vasospastic substance responsible for severe hypertension, which they called hypertensin. In those years, but following a different pathway, Irvine Page et al. arrived at the same conclusions almost simultaneously with the description of a substance called angiotonin. In all honesty, it was a shared discovery made simultaneously by the Argentine group and the group led by Irvine Page in USA. Finally, in 1957, the name angiotensin was applied, after a meeting between Braun Menéndez and Page.

Thus, the basic outline of the RAAS was established by the late 1950s, when the Skeggs group pronounced angiotensinogen as a renin substrate, after having described the existence of the angiotensin converting enzyme (ACE). The system has become more complex as new components were described. Angiotensin III (Ang III), also known as angiotensin 2-8, is the result of aminopeptidase A on Ang II. Angiotensin IV (Ang IV) or angiotensin 3-8 is derived from Ang III as the result of aminopeptidase N activity. Both components are active, and Ang III, as Ang II, can act on AT1 and AT2 receptors, whereas Ang IV would only target an insulin-regulated aminopeptidase. Angiotensin 1-7 (Ang 1-7) exhibits vasodilator and antiproliferative effects, produced by Ang I as the result of an endopeptidase, or by Ang II through the action of ACE, an enzyme that can also produce angiotensin 1-9 (Ang 1-9) from Ang I.

Interestingly, Ang (1-9) attenuates cardiomyocyte hypertrophy and fibrosis in hypertensive models, and these effects are blocked by the coadministration of an AT2 receptor antagonist. Due to the short half-life of these peptides, osmotic pumps are needed to maintain a therapeutic concentration. Accordingly, alternative delivery strategies are required for clinical translation. In this regard, Fattah et al. utilized, for the first time, a viral vector to mediate gene transfer of Ang-(1-9) into the heart and study the effects on post-infarction myocardial remodeling (Figure 1).

These researchers induced myocardial infarction without reperfusion in rats, performing a permanent ligation of the anterior descending coronary artery. Eight weeks after infarction, survival was greater in the viral vector group, together with increased ejection fraction and reduced fibrosis. In order to study the mechanisms that explain this improvement, the authors isolated cardiomyocytes and intracellular Ca++ was measured at baseline and after 15-minute acute incubation with Ang (1-9). Thus, they determined that the effects of Ang (1-9) are mediated via a direct positive inotropic effect, increasing sarcoplasmic reticulum Ca++ (SR Ca++) and Ca++ transient amplitude.

This study demonstrates that gene therapy, which increases Ang-(1-9) levels, a counter-regulator of RAAS in the heart, is beneficial on post-myocardial remodeling. Although the findings are original and interesting, future studies, especially in larger animal models subjected to infarction with reperfusion, would help to translate gene therapy to the clinical setting. Furthermore, the studies on cardiomyocytes were developed via acute peptide perfusion; further research is needed using myocytes from hearts infused in vivo with gene therapy.