EDITORIAL

Galectin-3 Associated With Post-Ischemic Ventricular Remodeling: Biomarker Role and Potential Therapeutic Applications

Asociación de la galectina-3 con la remodelación ventricular posisquémica: su rol como biomarcador y posibles aplicaciones terapéuticas

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Post-ischemic ventricular dilatation and cardiac remodeling refers to the changes in size, shape, structure and physiology of the heart after injury to the myocardium. Dilated cardiomyopathy from many causes results in a change in ventricular geometry, whereby the elliptical chamber becomes more spherical. This change in architecture alters myocardial fiber direction and diminishes function; extracellular matrix degradation contributes to this adverse LV remodeling. The early changes of increased spherical configuration lead to impairment of ventricular function and may lead to mitral valve regurgitation. Ventricular chamber dilatation and spherical deformation are important causes of morbidity and mortality of patients with congestive heart failure.

The cardiac extracellular matrix consists of a three-dimensional structural network of interstitial collagens to which other matrix components are attached. Collagen deposition is controlled and can be modulated by hormonal factors, growth factors, cytokines, regulatory proteins and/or hemodynamic factors. Increased collagen deposition is a prerequisite to prevent dilatation of the infarcted area. Excessive accumulation of collagen leads to ventricular diastolic and systolic dysfunction and ultimately contributes to heart failure. An appropriate balance of extracellular matrix synthesis and degradation is required for normal morphogenesis and maintenance of tissue architecture. An unbalance in the extracellular matrix turnover either by decreased matrix synthesis and/or increased degradation leads to cardiac dilatation or even rupture.

GALECTIN-3

The current issue of the Revista Argentina de Cardiología published the article « Effect of Galectin-3 Deficit on Ventricular Remodeling Following Coronary Occlusion in Mice" by Wilensky et al (1). The goal of this experimental study is to evaluate the role of genetic deletion of Gal-3 on early post-MI healing process, ventricular remodeling and function in mice. Importantly, the data set from this study could theoretically shed further light on whether galectin-3 levels could be used to improve patients' outcomes in early steps of post-ischemic heart failure.

Galectin-3 is a biomarker associated with inflammation and fibrosis that predicts adverse outcome and relates with extracellular matrix turnover in clinical heart failure. Whether galectin-3 is related to LV remodeling after acute myocardial infarction is unknown.

Weir et al. published in 2013 a clinical study (2): circulating galectin-3 and various extracellular matrix biomarkers were measured in 100 patients with acute myocardial infarction and LV dysfunction. Relationships among galectin-3, biomarkers, and LV remodeling were analyzed according to median baseline LV ejection fraction. Results showed that Galectin-3 was positively associated with remodeling only in patients with supramedian baseline LV ejection fraction (i.e. >49.2%; r=0.40; P=0.01) but not when LV ejection fraction was ≤49.2%. In addition Galectin-3 correlated significantly with matrix metalloproteinase-3 and monocyte chemoattractant protein-1 biomarkers at baseline. In conclusion, in this clinical study Galectin-3 correlated significantly with certain biomarkers involved in extracellular matrix turnover, although no definite relationship was identified with LV remodeling. Whether Galectin-3 plays a pathological role in remodeling remains unclear but merits further study.

MATRIX METALLOPROTEINASES (MMPS)

Matrix metalloproteinases (MMPs) are endopeptidases than can cleave all components of the extracellular matrix and consequently participate in left ventricle remodeling. The expression of metalloproteinase 9 (MMP9) is implicated in the degradation of extracellular matrix and myocardial remodeling. Extracellular matrix (ECM) degrading enzymes expressed after myocardial infarction belong to the families of serine and MMPs and are secreted as latent proenzymes that have

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to be activated. It is crucial to keep the activity of these enzymes under tight control by either influencing the synthesis, activation or inhibition by tissue inhibitors of MMPs (TIMPs) or alpha2-macroglobulin. Regulating the balance of extracellular matrix remodeling either by extracellular matrix synthesis or degradation might be one of the possible prevention mechanisms for heart failure.

Levels of MMPs are increased after myocardial infarction, and inhibition of MMPs and MMP-null mice have demonstrated a direct relationship between MMPs and left ventricle remodeling (3, 4). Particularly, MMP-9 is a gelatinase importantly upregulated after myocardial infarction and its gene deletion attenuates left ventricle remodeling (5). Hence, MMP-9 contributes to adverse left ventricle remodeling post-myocardial infarction. Furthermore, studies of infarct rupture in patients have also demonstrated that MMP9 is expressed by inflammatory cells in the infarcted area (6).

FIBRONECTIN, INTEGRINS, RGD PEPTIDES

The ECM not only connects cells together in tissues, but also guides their movement during wound healing and embryonic development. One essential component of the ECM is the protein fibronectin that assembles into fibrils attaching cells to the ECM. Cells bind and exert forces on fibronectin through transmembrane receptor proteins of the integrin family, which mechanically couple the actin cytoskeleton to the ECM via an elaborate adhesion complex. Naturally, the binding between integrin and fibronectin must sustain significant force in order to transmit force signals. Fibronectin and physical forces linked to the geometry of extracellular environments influence the rearrangement of the contractile apparatus. The aspargine-glycine-aspartic acid-serine (RGDS) motif of fibronectin has a critical role during fetal cardiac development, and might be upregulated in pathophysiological conditions, such as shear stress and after infarction (7).

MANAGEMENT OF ADVERSE REMODELING

Current therapeutic research is focused on investigating the strategy of combining genetic engineering, tissue engineering materials, and stem cell transplantation to improve ischemic cardiomyopathy patient outcome. Strategies to repair or regenerate injured cardiac tissue may offer new hope for the treatment of congestive heart failure and play an important role in modern cardiology.

Treatment of large chronic heart damage with possibility of regaining hemodynamic performance should consider the following approaches: 1) reduce/remove the scar; 2) recover ventricular shape, from spherical to conical; and 3) increase the presence of functional cardiomyocytes and angiogenesis, to both stop the cardiac insufficiency and eventually recover function. The functional recovery could be a consequence of intrinsic and extrinsic processes initiated by the reduction of scar size and fibrosis density (regenerative treatment) and the effect promoted by external tissue engineering approaches (extrinsic treatment) (8, 9).

BIOARTIFICIAL MYOCARDIUM & BIOPROSTHESES FOR VENTRICULAR SUPPORT AND MYOCARDIAL REGENERATION

Regeneration of the vascular and cardiomyocyte network might be a potential new treatment for heart failure patients.

The association of stem cells and elastomeric scaffolds raises the expectations of achieving the repair of the myocardial tissue and avoiding ventricular chamber dilation. Biohybrid patches representing "Bioartificail Myocardium" could provide a supporting band-aid effect, limiting the spread of the infarcted areas and reinforcing the ventricular wall to yield stress tolerance by a passive girdling effect of the patch and improving strain distribution along the ventricular wall, while reducing cell apoptosis by the paracrine effect of the grafted stem cells.

Recently, the RECATABI European Study, http://www.recatabi.com (REgeneration of CArdiac Tissues Assisted by Bioactive Implants) demonstrated the feasibility and safety of Bioartificial Myocardium created for the treatment of myocardial infarction (10, 11). Our myocardial tissue engineered approach showed beneficial effect in terms of reducing the number of inflammatory cells expressing MMP9 and thus, diminishing the cardiac remodeling.

Following these studies "Ventricular Support Bioprostheses" were designed for left ventricular and/or right ventricular support and regeneration, including different sizes for partial (patch of) or complete ventricular wrapping, with implant characteristics (mechanical, physical, chemical, and biological) adapted for the left or right ventricular geometry, physiology, and pathology. Ventricular bioprostheses should avoid heart transplantation or offer a relatively secure mid- to long-term bridge to heart transplant allowing critically ill patients to significantly improve their quality of life while waiting for a heart donor (12).

Conflicts of interest

None declared.

(See authors' conflicts of interest forms in the website/Supplementary material).

REFERENCES

1. Wilensky L, Martínez Naya NI, Cassaglia P, Volberg V,Tau J, Aruanno E, et al. Effect of Galectin-3 Deficit on Ventricular Remodeling After Coronary Occlusion in Mice. Rev Argent Cardiol 2015;83:287-291. http://dx.doi.org/10.7775/rac.v83.i4.5977

2. Weir RA, Petrie CJ, Murphy CA, Clements S, Steedman T, Miller AM, et al. Galectin-3 and cardiac function in survivors of acute myocardial infarction. Circ Heart Fail. 2013;6:492-8. http://doi.org/6kt

3. Rohde LE, Ducharme A, Arroyo LH, Aikawa M, Sukhova GH, Lopez-Anaya A, et al. Matrix metalloproteinase inhibition attenuates early left ventricular enlargement after experimental myocardial infarction in mice. Circulation 1999;15:3063-3070. http://doi.org/6kv

4. Yarbrough WM, Mukherjee R, Escobar GP, Mingoia JT, Sample JA, Hendrick JW, et al. Selective targeting and timing of matrix metalloproteinase inhibition in post-myocardial infarction remodeling.

Circulation 2003;108:1753-1759. http://doi.org/cfcf8x
5. Ducharme A, Frantz S, Aikawa M, Rabkin E, Lindsey M, Rohde LE, et al. Targeted deletion of matrix metalloproteinase-9 attenuates left ventricular enlargement and collagen accumulation after experimental myocardial infarction. J Clin Invest 2000; 106:55-62. http://doi.org/ft4srj
6. van den Borne SW, Cleutjens JP, Hanemaaijer R, Creemers EE, Smits JF, Daemen MJ, et al. Increased matrix metalloproteinase-8 and -9 activity in patients with infarct rupture after myocardial infarction. Cardiovasc Pathol 2009;18:37-43. http://doi.org/dntcxc
7. Schussler O, Coirault C, Louis-Tisserand M, Al-Chare W, Oliviero P, Menard C, et al. Use of arginine-glycine-aspartic acid adhesion peptides coupled with a new collagen scaffold to engineer a myocardium-like tissue graft. Nat Clin Pract Cardiovasc Med 2009;6:240-9. http://doi.org/b35fhr
8. Chachques JC, Trainini JC, Lago N, Masoli OH, Barisani JL, Cortes-Morichetti M, et al. Myocardial assistance by grafting a new bioartificial upgraded myocardium (MAGNUM clinical trial): one year follow-up. Cell Transplant 2007;16:927-34. http://doi.org/cx4vs9
9. Shafy A, Fink T, Zachar V, Lila N, Carpentier A, Chachques JC. Development of cardiac support bioprostheses for ventricular restoration and myocardial regeneration. Eur J Cardiothorac Surg 2013; 43:1211-9. http://doi.org/6kw
10. Soler-Botija C, Bagó JR, Llucià-Valldeperas A, Vallés-Lluch A, Castellas-Sala C, Martínez-Ramos C, et al. Engineered 3D bioimplants using elastomeric scaffold, self-assembling peptide hydrogel, and adipose tissue-derived progenitor cells for cardiac regeneration. Am J Transl Res 2014;6:291-301.
11. Martínez-Ramos C, Rodríguez-Pérez E, Garnes MP, Chachques JC, Moratal D, Vallés-Lluch A, et al. Design and assembly procedures for large-sized biohybrid scaffolds as patches for myocardial infarct. Tissue Eng Part C Methods 2014;20:817-27. http://doi.org/6kx
12. Chachques JC, Pradas MM, Bayes-Genis A, Semino C. Creating the bioartificial myocardium for cardiac repair: challenges and clinical targets. Expert Rev Cardiovasc Ther 2013;11:1701-11. http://doi.org/6kz