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New insights into microRNA and cardiac allograft fibrosis

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Advances in immunosuppressive drug treatment, surgical procedures, organ preservation and other medical treatments have improved the outcome for and survival of heart-transplant patients. Despite these advances, graft rejection and its complications remain a barrier to long-term graft survival. In addition to acute graft rejection and coronary allograft vasculopathy, cardiac allograft fibrosis is a major cause of progressive loss of graft function. Although multiple factors are associated with cardiac fibrosis, the aetiology of this disease remains poorly understood and effective treatment is limited.

The recent publication "miR-21 promotes fibrosis in an acute cardiac allograft transplantation model" by Gupta et al. investigated the relationship of microRNAs and cardiac allograft fibrosis[1]. In a murine heterotopic heart transplantation model, Gupta et al. confirmed miR-21 as an important regulator of allograft fibrosis. In biopsies of transplanted human hearts with rejection, miR-21 was also induced. IL-6, which is a well-known cytokine involved in fibrosis, mediates its pro-fibrotic effects via miR-21. Furthermore, miR-21 was shown to induce the transformation of monocytes to fibrocytes while both the genetic and pharmacological inhibition of miR-21 successfully reduced fibrosis and fibrocyte accumulation in cardiac allograft.

The recent discovery of miRNAs is an important breakthrough in biology. Their role in development, physiology and pathology is beginning to emerge as we start to identify their biological functions in different conditions. Numerous studies have described changes in miRNA expression in diseased human hearts and vascular tissues, including myocardial infarction, cardiac hypertrophy, heart failure, angiogenesis, vascular stenosis and fibrosis. One of these miRs is miR-21, as is highly expressed in cardiomyocytes[2], cardiac fibroblasts[3], vascular smooth muscle cells[4] and endothelial cells[5]. Studies into the gain and loss of function have uncovered prominent roles for miR-21 in diverse cardiovascular diseases such as myocardial infarction, heart failure and cardiomyopathies[6]. However, the role of microRNAs during heart transplantation had remained unknown. The results from Gupta et al have added another piece to the puzzle and paved the way for a targeted molecular-level therapy against cardiac allograft fibrosis.

The recent success of the first in-human clinical trial of an miRNA therapeutic for treating

hepatitis C virus, has opened the door for a new class of therapeutics[7]. However, before scientists and clinicians can begin to target miR-21 in this manner, hurdles need to be overcome. MiR-21 manipulation can lead to broad alterations in regulatory pathways at multiple levels and tissues because it is universally expressed in mammalian organ systems such as the heart, spleen, small intestine and colon[8]. There is mounting evidence for the involvement of miR-21 in cell proliferation, inflammation, fibrosis and dysplasia[9]. MiR-21 inhibitors can, for example, influence neuron proliferation[10] and macrophage activation[11] as well as cause suppression of extracellular matrix production. In addition, a recent study showed that therapeutic systemic inhibition of miR-21 to prevent myointimal hyperplasia was associated with impaired kidney function[12]. It is therefore necessary to reveal the global pathways of miR-21 and the overall consequences of its modulation before decisions are taken precipitately. Nevertheless, the work carried out by Gupta et al. is an important pilot study for future work on developing novel targeted anti-fibrotic treatment for cardiac organ transplantation, which will eventually be translated into clinical therapies.

About the author

Dr. Dong Wang, MD, is currently a Postdoctoral Fellow at the Transplant and Stemcell-Immunobiology Lab at the University of California, San Francisco (UCSF). He obtained his medical degree in the University of Hamburg, Germany. Dr. Wang was a recipient of the ISHLT Travelling Scholarship 2014 and finalist at the Philip K. Caves Award Session 2015.