MARTÍN DONATO [MTSAC]

Avoiding Cardiac Senescence

Gonzalez-Valdes I, Hidalgo I, Bujarrabal A, Lara-Pezzi E, Padron-Barthe L, P. Garcia-Pavia P, et al. Bmi1 limits its dilated cardiomyopathy and heart failure by inhibiting cardiac senescence. **Nature Communications 2015;6:6473. doi:10.1038/ncomms7473.**

Dilated cardiomyopathy (DCM) is the most frequent cause of non-ischemic cardiomyopathy often leading to heart failure and sudden death. Despite its relevance, the mechanisms underlying this disease are not fully known, although 20% to 50% of cases are considered to have a genetic origin associated to gene mutations (changes in DNA sequences) of cardiac structural proteins. Challenging this hypothesis, the study published by González-Valdez et al in Nature Communications shows that DCM can also develop as a result of epigenetic changes (altered chromatin folding) not affecting DNA sequence but the level of gene expression.

Researchers from the National Cardiovascular Research Center [Centro Nacional de Investigaciones Cardiovasculares (CNIC)] led by Dr. Susana González have identified the presence of Bmi1 protein in the heart which, among other properties, prevents the aging process (senescence) of cardiac cells, protecting the heart from developing DCM. Bmi1 belongs to an important family of proteins called Polycombs which regulate the expression of numerous genes by changing chromatin folding during DNA transcription. This protein is a key factor in the process of cell aging and in the maintenance and renovation of many tissues, and consequently has a direct effect on mammalian survival.

In the present study, transgenic Bmi1 mice models were developed with specific Bmi1 functional suppression in the heart. As a result, mice suffered left ventricular dilatation that produced severe functional impairment leading to acute pulmonary edema and sudden death. Experimental results indicate that Bmi1 absence induces changes in chromatin folding allowing the expression of certain genes that had previously been silenced or turned-off, as the senescence marker p161NK4a. These changes produce the secretion of a series of SASP factors inducing a senescent or no-answer state in adult cardiac cells which contribute to cardiac muscle alterations and DCM. Therefore, the authors of this study postulate a new mechanism to explain the development of DCM, emphasizing the relevance of the p161NK4a gene as a marker of cardiac aging.

In addition, another important finding is that DCM can be reversed by the administration of plasma from healthy to diseased animals, suggesting the existence of soluble factors in the blood of healthy individuals capable of regressing critical structural and molecular aspects of cardiac aging.

Dr. González´s team results contribute to understand the molecular mechanisms that explain cardiac senescence and therefore age-related cardiovascular diseases. These findings have a potential impact on clinical practice. In addition to providing new targets for the diagnosis of DCM, they suggest that the modulation of the cardiac senescent response by reprogramming the epigenetic mechanisms of the heart is a new strategy for the treatment of heart failure, turning Bmi1 as an attractive therapeutic goal.