The source of adipocytes in arrhythmogenic cardiomyopathy

Arrhythmogenic Cardiomyopathy (ACM) is a genetic disorder characterized by progressive fibro-fatty substitution of the heart, arrhythmias and sudden death. It affects mainly young people and athletes. The clinical manifestations, often devious in early phases, are variable. The pathogenic mechanisms are still unclear. It is known that the causative genetic mutations involve mainly genes coding for desmosomes. Desmosomes are cellular junctions, responsible of the physical interaction between cells subjected to high mechanical stretch, mainly cardiomyocytes and epithelial cells.

Fibro-fatty substitution is the hallmark of the disease but, until now, the cellular component responsible of this replacement it was not clear. Many cellular types have been studied but for all of them some limits were recognized. In particular, contractile cells has been the focus of attention till now, since highly expressing desmosomes. The urgency of a clarification about the mechanisms of fibro-fatty substitution is relevant because progressive adipocytes deposition leads both to arrhythmias exacerbation and to loss of cardiac contractility, ultimately resulting in heart failure.

Cardiac mesenchymal stromal cells (C-MSC) are the most abundant cells in the heart. They are able to differentiate into various cell types, including adipocytes. They are supportive cells and they play a critical role in maintaining normal cardiac function, as well as in cardiac remodeling during pathological conditions.

In a new study, conducted at Centro Cardiologico Monzino-IRCCS, we demonstrated the role of C-MSC in ACM adipose substitution in human hearts. We performed staining on serial slices of ACM and control explanted hearts using Perilipin1 (PLIN1) antibody, specific for adipocytes, CD29 and CD105, that are mesenchymal markers. We obtained mesenchymal markers positive cells in active differentiation to adipocytes (presenting many small fat droplets surrounded by adipocytes-specific PLIN1).

Moreover we isolated C-MSC from right ventricular bioptic samples from ACM patients and control subjects. We demonstrated that they express desmosomal genes and that ACM C-MSC are more prone than controls to differentiate into

Elena Sommariva *and* ***Ilaria Stadiotti***
Centro Cardiologico Monzino IRCCS
Milan, Italy

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