RELAZIONE ORALE

OVERCOMING HORMONAL BARRIERS TO CARDIAC REGENERATION

G. D'Uva[1|2]

[1]*Department of Medical and Surgical Sciences;* [2]*IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy*

Cardiomyocyte loss after acute or chronic myocardial injury is a major cause of heart failure. Adult mammalian cardiomyocytes retain a very limited proliferative capacity, insufficient for effective regeneration. A key goal in cardiac regenerative medicine is therefore to stimulate endogenous cardiomyocytes to re-enter the cell cycle and form new functional myocardium. Several regenerative growth factors have been shown to partially reactivate this potential [1]. Endogenous hormones also regulate cardiac regeneration, with glucocorticoids acting as systemic inhibitors [2]. We recently found that glucocorticoids broadly suppress cardiomyocyte proliferation induced by regenerative growth factors and cytokines [3].

Mechanistically, glucocorticoid receptor activation induces the expression of MAPK-ERK pathway inhibitors DUSP1 and ERRFI1, reducing ERK activation, nuclear translocation, and downstream regenerative transcriptional programmes. Genetic or pharmacological inhibition of DUSP1 or ERRFI1 attenuates this glucocorticoid-mediated suppression.

We further demonstrated that the postnatal increase in glucocorticoid receptor signalling contributes to the loss of regenerative competence, whereas glucocorticoid receptor antagonism reinstates cardiomyocyte responsiveness to mitogenic stimuli in juvenile and adult settings. In vivo, combining glucocorticoid receptor inhibition with growth factors, such as Neuregulin 1, enhances cardiomyocyte proliferation, reduces DNA damage and preserves cardiac function in a mouse model of cardiac injury.

Together, these findings reveal a previously unrecognized endocrine brake on cardiac regeneration and identify transient glucocorticoid receptor antagonism as a promising strategy to potentiate growth-factor-based therapies for heart repair.

References

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