Abstract: P280

Myocardial resistance against proteotoxicity

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Introduction - Protein quality is assured at a cellular level by a finely tuned biological machinery called unfolded protein response (UPR) devoted to recognize, unfold, and refold abnormally arranged proteins. A growing set of previously unrelated disorders has been associated to adverse effects deriving from the accumulation of non-functional aggregates of unfolded proteins named oligomers. Those can perturb the homeostasis, and ultimately the survival of the cell itself. As far as the heart is concerned, an elevated oligomer presence was detected within the myocardium of idiopathic dilated cardiomyopathy (iDCM) cases compared to matched controls.

Purpose – A defective UPR system in the myocardium of iDCM could represent a possible biological foundation leading to or a consequence of a toxic proteic buildup.

Methods - Lysates from left ventricle specimens of iDCM (n=8), and matched control cases (n=8) were employed for transcript and protein analysis in order to evaluate components of the UPR system. Both groups were subdivided into young and old subjects (n=4 for each subgroup).

Results – Young and old subgroups mean ages for iDCM subjects were 30 and 58.8 respectively and 29.5 and 56.8 for controls. Men and women were equally represented in every subgroup. Significant differences (P <0.05) and diverse defects along the pathway were detected by comparing same age subjects. Young iDCM patients showed a significant increase in PERK as well as CHOP, Caspase-12 and the spliced form of XBP-1. Consistent with previous findings Proteasome 20S5ß was found to be diminished. On the other hand, older iDCM cases expressed significantly lower levels of spliced XBP-1, ATF6 ratio and higher levels of ATF4 and eIF2a. In addition, significant differences with aging were appreciated throughout the pathway in control subjects in contrast with the iDCM cohort.

Conclusion - These findings shed light on the pivotal role of proteotoxicity overwhelming UPR control as an additional etiology of heart failure. The combined alteration of several target proteins of this pathway configures as a condition of misfolded peptides accumulation ultimately exhausting the cell survival capabilities.