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Heart failure (HF) is a progressive debilitating condition where loss of contractile function results in severe disability and death. In a subset of cases, clustered as “Dilated Cardiomyopathy” (DCM), the origin of the HF is unknown. Despite increasing knowledge of the molecular mechanisms of HF, the pathogenetic mechanisms that give rise to DCM are unknown. The progressive pathologic misfolding of proteins has been identified to be at the origin of many chronic diseases such as systemic amyloidosis, cystic fibrosis, emphysema, diabetes, muscular dystrophy and neurodegenerative diseases. We propose that protein misfolding may be the pathogenetic basis for some forms of DCM as suggested by the presence of protein aggregates within the cells.

We show that, in samples of failing heart tissue from idiopathic DCM, cytoplasmatic aggregates are present in greater quantities than seen in normal aging. Immature forms of the fibrils, the presumably toxic oligomeric fibrils, are also present in the failing hears. Our data also suggest that those changes are not present due to post mortem changes nor are they linked only to end stage heart failure, since they are also seen in biopsy tissue from earlier stages of heart failure in humans.

An important fraction of protein synthesis, folding and post translational modifications occur inside the sarco-endoplasmic reticulum (SR). In cardiomyocytes, the SR has the dual role of modulating contractility through rhythmic changes in Ca^{2+} levels while maintaining constant Ca^{2+} levels for the control of protein synthesis and processing. Abnormal SR Ca^{2+} homeostasis is a well characterized feature in failing hearts and it might result and/or determine protein misfolding. Changes in the expression levels of the proteins controlling protein folding and degradation suggest a condition of SR stress and protein misfolding.

In conclusion we propose that protein misfolding can be an important pathogenetic mechanism leading to early cardiac dysfunction and later heart failure. Changes in protein folding function can be detected at initial stages and the identification of early markers will help to improve the preventive screening and early treatment.