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Improving cardiac protein quality control as a novel therapeutic strategy

Targeted removal of damaged/misfolded proteins in the cell is primarily performed by the ubiquitin-proteasome system (UPS). When escaped from UPS-mediated degradation, misfolded proteins tend to form aberrant aggregates which are no longer accessible by the proteasome and are generally believed to be removed by macroautophagy. Remarkable accumulation of myocardial ubiquitinated proteins and autophagosomes are observed in human heart failure of nearly all causes, indicative of UPS and autophagic dysfunction in the development of cardiac failure. The creation of stable cell lines, adenoviruses, and stable transgenic mice expressing a surrogate UPS substrate, such as green fluorescence protein (GFP) modified by fusion with degron CL1 (known as GFPu or GFPdgn), has made it possible and convenient to monitor dynamic changes in UPS performance in situ or in vivo, and thereby enabled my lab to demonstrate for the first time in intact animals that increases in misfolded proteins and resultant aberrant protein aggregation impair UPS function and cause proteasome functional insufficiency (PFI). Similarly, we and collaborators detected cardiac UPS functional insufficiency in acute ischemia/reperfusion (I/R), chronic pressure overload, and diabetic cardiomyopathy. Using both gain- and loss-of-function approaches, we were able to demonstrate that PFI is a major factor underlying UPS malfunction and plays an important pathogenic role in heart disease with increased proteotoxic stress such as proteinopathy, I/R injury and diabetic cardiomyopathy in mice. Furthermore, we have discovered that cGMP-dependent kinase (PKG) positively regulates the proteasome in cardiomyocytes, PKG activation by either genetic or pharmacological means, such as phosphodiesterase 5 (PDE5) inhibition, promotes proteasome-dependent degradation of a surrogate and a bona fide misfolded protein in cardiomyocytes, and PDE5 inhibition by sildenafil reduces misfolded protein abundance and aggregation and slows down disease progression in a well-established mouse model of cardiac proteinopathy. We have also collected strong evidence that the protection of PDE5 inhibition against I/R injury depends largely on improving proteasome function. Muscarinic receptor activation can enhance cardiac proteasomal function in a PKG dependent manner. These findings demonstrate the feasibility to use pharmacological method to enhance UPS-mediated degradation of misfolded proteins and thereby to treat heart disease with elevated misfolded proteins. A good body of evidence has also demonstrated that increasing autophagy is beneficial to the treatment of most heart diseases. Hence, improving cardiac protein quality control through UPS enhancement and increasing autophagic flux has emerged as a promising novel therapeutic strategy warranted for translational studies.

Biography

Dr. Wang had studied/worked in biomedicine for 14 yrs in Wuhan, China. He was appointed Assistant Professor in 2001, promoted to Associate Professor in 2005, tenured in 2006, and became full Professor and Director of the MD/PhD program in 2006. Basic biomedical sciences: biochemistry and molecular biology, anatomy, histology and physiology, cell biology and transgenics. Dr. X-J Wang's research laboratory is primarily funded by NIH R01 grants and focuses on protein quality control and degradation in cardiovascular physiology and pathophysiology, molecular mechanisms of the progression from primary heart diseases to congestive heart failure, and molecular pathogenesis of misfolded proteins.

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