Heart failure is a devastating condition affecting millions of people globally with a rising prevalence due to an expansion of the ageing population and epidemics of obesity, diabetes and hypertension. Despite numerous causative factors, the majority of heart failure cases are the consequence of massive cardiomyocyte loss. As cardiomyocytes hold very little potential in replication, exquisite regulation of cellular homeostasis and integrity reliant on protein quality control is crucial for cardiomyocyte survival and function, particularly under stress. A major site of protein quality control is the endoplasmic reticulum (ER). The endoplasmic reticulum is the site for synthesis and folding of secreted and membrane-bound proteins, which account for 1/3 of total proteins. Loss of ER homeostasis and function culminates in a greater risk of cardiomyocyte death and it has been shown that detrimental ER stress underlies the pathogenesis of many forms of heart disease.

With the aim to uncover novel ER stress regulation mechanisms, we examined the expression pattern of p21activated kinase 2 (Pak2) in cardiomyocytes and myocardium across species. We investigated its role in cardioprotection using Pak2 cardiac deleted mice (Pak2-CKO) under ER stress conditions. Molecular elucidation unveiled a new mechanism by which Pak2 promoted the protective ER stress response. The translational relevance of this protective mechanism was evaluated in human induced pluripotent stem cells-derived cardiomyocytes (iPSC-CMs), and the therapeutic potential was explored by inducing Pak2 activation using a genetic approach or AAV9-based gene delivery.

We found that Pak2 was an ER-resident stress-responsive kinase in cardiomyocytes, and showed that Pak2-CKO mice under stress manifested defective ER response, cardiac dysfunction and profound cell death. Pak2 loss-induced cardiac damage was an ER-dependent event. Mechanistic studies in rat cardiomyocytes and human iPSC-CMs, revealed that Pak2 regulation of protective ER function was via the IRE1/XBP1s-dependent pathway. Therapeutically, Pak2 activation was capable of strengthening ER function, improving cardiac performance and diminishing apoptosis, thus protecting the heart from failure. Our findings reveal a novel ER-centered cardioprotective mechanism, which promotes the protective ER stress response via modulation of Pak2: this novel therapeutic strategy may be used to treat cardiac disease and heart failure.