Project Title: FBXL5, role in embryonic stem cells differentiation towards cardiac cells

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Summary: (1000 characters)

Genetic alterations of the transcriptional regulators CITED2, HIF-1α (hypoxia-inducible factor-1α) or p300, in mouse models, result in cardiovascular defects [1-4]. In addition, CITED2 and HIF-1 are important for self-renewal and cardiac differentiation of embryonic stem cells (ESC) [5]. Recently, we showed that the E3 ubiquitin ligase FBXL5 modulates the transcriptional activity of HIF-1α through the degradation of CITED2, controlling HIF-1α access to its co-activators p300/CBP [6]. In mouse ESC, FBXL5 overexpression decreases CITED2 expression and triggers the expression of mesoderm and endoderm early markers, suggesting a spontaneous differentiation [6]. Interestingly, the stability and function of FBXL5 are dependent on iron and oxygen availability, and both non-physiological hypoxia and/or iron cardiac contents are risk factors for congenital cardiovascular defects [1]. Moreover, recent evidence indicated that FBXL5 may play a role in mouse cardiovascular development. We hypothesize that the FBXL5-CITED2-p300/CBP-HIF-1α protein network is involved in normal cardiogenesis, and may be critical for the fine-tuning of HIF-1α transcriptional activity during this process. In the present proposal, we intend to investigate the role of FBXL5 within this protein network, ant its function during cardiac differentiation of mouse ESC.

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(* indicates Joint first co-authors)

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