Cullin-associated and neddylation-dissociated 1 protein (CAND1) governs cardiac hypertrophy and heart failure partially through regulating calcineurin degradation

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1. 簡述論文的重大發現：

病理性心臟肥大的主要成因是蛋白質的生成-降解平衡失衡。其中 Cullin-associated and neddylation-dissociated 1 protein (CAND1)是一個調節蛋白質降解機制中的 coordinator，透過促進 cullin1/atrogin1/calcineurin complex 的形成，來增加對 Calcineurin 的泛素化和降解。透過抑制 calcineurin /NFAT pathway，進而促進維持心肌細胞中正常的蛋白質穩定狀態，緩解 pressure overload 導致的心臟肥大和心衰竭。

此研究發現在 CAND1-KO$^{+/-}$(Heterozygous knock-out)組別或 CAND1 overexpression 組別都不影響正常健康小鼠的心臟功能狀態。但在透過 Transverse aortic constriction(TAC)誘導心肌肥大和心衰竭的小鼠發現，CAND1-KO$^{+/-}$會加重心臟惡化的程度，而且病情惡化很快，有較高的死亡率，不像典型的慢性心衰竭。相反的，CAND1 overexpression 則對心臟損傷產生了顯著的保護作用。另外，腺病毒介導的 CAND1 overexpression，也有效改善了 TAC 誘導小鼠的心臟肥大和心衰竭，結果顯示，CAND1 可能是心臟肥大和心衰竭的潛在治療目標。

2. 對論文內容的提問：

Calcineurin 是調節心臟肥大相關的蛋白之一，但同時 Calcineurin 也是啟動 T 細胞免疫相關的重要因子，此篇作者研究 CAND1 在心肌細胞中促進 Calcineurin 的降解，但並不清楚是否會影響 Calcineurin 的免疫相關作用。

3. 論文的缺點與評論：

若有進一步的實驗研究，驗證 CAND1 是否會影響 Calcineurin 的免疫相關作用，將更有助於了解 CAND1 未來用於治療心臟肥大和心衰竭的潛在可能性。

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Cullin-associated and neddylation-dissociated 1 protein (CAND1) governs cardiac hypertrophy and heart failure partially through regulating calcineurin degradation

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ABSTRACT

Pathological cardiac hypertrophy is a process characterized by significant disturbance of protein turnover. Cullin-associated and Neddylation-dissociated 1 (CAND1) acts as a coordinator to modulate substrate protein degradation by promoting the formation of specific cullin-based ubiquitin ligase 3 complex in response to substrate accumulation, which thereby facilitate the maintaining of normal protein homeostasis. Accumulation of calcineurin is critical in the pathogenesis of cardiac hypertrophy and heart failure. However, whether CAND1 titrates the degradation of hypertrophy related protein eg. calcineurin and regulates cardiac hypertrophy remains unknown. Therefore, we aim to explore the role of CAND1 in cardiac hypertrophy and heart failure and the underlying molecular mechanism. Here, we found that the protein level of CAND1 was increased in cardiac tissues from heart failure (HF) patients and TAC mice, whereas the mRNA level did not change. CAND1-KO+ /- aggravated TAC-induced cardiac hypertrophic phenotypes; in contrast, CAND1-Tg attenuated the maladaptive cardiac remodeling. At the molecular level, CAND1 overexpression downregulated, whereas CAND1-KO+ /- or knockdown upregulated calcineurin expression at both in vivo and in vitro conditions. Mechanistically, CAND1 overexpression favored the assembly of Cul1/atrogin1/calcineurin complex and rendered the ubiquitination and degradation of calcineurin. Notably, CAND1 deficiency-induced hypertrophic phenotypes were partially rescued by knockdown of calcineurin, and application of exogenous CAND1 prevented TAC-induced cardiac hypertrophy. Taken together, our findings demonstrate that CAND1 exerts a protective effect against cardiac hypertrophy and heart failure partially by inducing the degradation of calcineurin.

Non-standard abbreviations and acronyms: ANF, Atrial natriuretic factor; β-MHC, β-myosin heavy chain; UPS, Ubiquitin-proteasome system; CRLs, Cullin-RING family of ubiquitin ligases; FBP, F-box protein; CSN8, COP9-signalosome subunit 8; CSN5, COP9-signalosome subunit 5; CAND1, Cullin Associated And Neddylation Dissociated 1; HF, Heart failure; α-MHC, α- myosin heavy chain; Tg, Transgenic; NFATc3, Nuclear factor of activated T cells; LVIDd, LV internal dimension at end-diastole; LVIDs, LV internal dimension at systole; EF, Ejection fraction; FS, Fractional shorting; AAV9, Adneo-associated virus-9; CQ, Chloroquine; BAF, Bafilomycin A1; TBIP120A, TBP-interacting protein 120 A.

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