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RB AND P130 CONTROL THE POST-MITOTIC PHENOTYPE IN ADULT HEART MUSCLE BY RECRUITING THE HETEROCHROMATIN PROMOTING FACTOR HP1γ TO GROWTH ASSOCIATED GENES

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[1]Yaping Wang, [2]Jian'an Wang. *[1]Cardiovascular Center; [2]Cardiovascular Key Lab of Zhejiang Province, Second Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, 310009, P. R. China*

Objectives Although the regenerative potential of the heart is a matter of debate, normal adult cardiac myocytes (ACM) are post-mitotic and E2F-dependent genes involved in G2/M and cytokinesis are stably repressed. However, the mechanisms underlying this silencing are unknown. Heterochromatin formation, which increases during cardiac differentiation, can regulate transcriptional silencing in a retinoblastoma protein (Rb)/E2F-dependent fashion.

Methods Iducible, cardiac-specific Rb and p130 double-knockout (IDKO) mice were created to investigate whether Rb or Rb-family member p130, specifically regulate the postmitotic state of ACMs. We compared G2/M and cytokinesis related genes by RT-PCR, heterochromatin formation by confocal analysis and HP1γchanges in G2/M and cytokinesis related genes by Chip between ACMs and IDKO ACMs.

Results ACMs within IDKO hearts lost their heterochromatin and up-regulated G2/M and cytokinesis related genes. IDKO ACMs spontaneously proliferated leading to 30% increased heart size within 3 weeks. It has been suggested that irreversible gene silencing by Rb family members is related to their ability to recruit HP1 to the promoters of E2F-dependent genes resulting in their incorporation into heterochromatin. In ACMs, depletion of HP1γ up-regulates expression of G2/M and cytokinesis genes. HP1γ is associated with promoters of G2/M and cytokinesis genes in ACMs; however, this binding was not detected in IDKO ACMs.

Conclusions Thus, Rb and p130 have overlapping roles in maintaining the postmitotic state of ACMs, through their interaction with HP1γ to direct heterochromatin formation and silencing of proliferation associated genes.