Review of: "Polycomb group protein CBX7 represses cardiomyocyte proliferation via modulation of the TARDBP/Rbm38 axis"

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Summary

This study investigated how postnatal cardiomyocytes (CMs) lose proliferative capacity. The authors found that the expression of a polycomb group protein CBX7 increased in the heart soon after birth. Ectopic expression of CBX7 by using adenoviral particles reduced the level of proliferation markers in cultured neonatal CMs. They generated conditional knockout mouse lines to inhibit CBX7 expression in CM-specific manner and found that the level of proliferation markers increased in CMs *in vivo* along with interesting phenotypes such as neonatal lethality, cardiomegaly, and thickening of myocardial walls. For their molecular mechanism studies, they found that CBX7 interacts with TARDBP, an RNA-binding protein. Among multiple targets of TARDBP, another RNA-binding protein RBM38 gene expression was positively regulated by CBX7. RBM38 is a well-known cell cycle repressor and its overexpression resulted in reduced proliferation of CMs *in vitro*. The authors claimed that CBX7 inhibits CM proliferation by interacting with TARDBP and thus by affecting RBM38 gene expression.

There are a few minor concerns with this study which include the following:

1. This study showed that targeted inhibition of CBX7 led to reduced mass per area of myocardium in Figure 1F-G. This nature of porous and sponge-like myocardium is seen in the developing fetal heart, and left ventricular non-compaction (LVNC) cardiomyopathy. The relationship between CM proliferation and LVNC has been controversial. It would be better to discuss how findings from this study align with or disagree with previous reports about LVNC in the context of CM proliferation.

2. TARDBP was discovered as an important protein in the pathogenesis of amyotrophic lateral sclerosis (ALS). Studies found that TARDBP forms insoluble aggregates or so-called stress granules (SGs) in the cytoplasm, leading to death of motor neurons. The current study showed that TARDBP interacts with CBX7, and the staining pattern was speckled in the heart (Figure S10). The authors need to discuss the potential mechanisms of how stress granules formed by TARDBP and CBX7 can affect proliferation of CMs.

3. Although the interaction between TARDBP and CBX7 was examined with MEFs and heart tissue, they did not include CMs. It would be more convincing if they validate the interaction by utilizing isolated CMs or a CM cell line HL-1.

4. Even though ectopic expression of RBM38 reduced CM proliferation in Figure 5H, it is still unclear how RBM38 inhibits CM proliferation. It would be better to show whether RBM38 gain-of-function leads to increased Cdkn1 expression in CMs.

5. It would be more significant if they showed co-localization of Rbm38 mRNA with CBX7 or TARDBP in the heart through *in situ* hybridization methods.