ijms-2505736 Round 1 Review

RNA-binding proteins as critical post-transcriptional regulators of cardiac regeneration

Overall Recommendations: Minor revisions

General Comments:

The author is to be commended for tackling a complex subject and one as important as cardiac regeneration. Studies on cardiac stem cells have produced very little of therapeutic value over the last 15 years so other methods of initiating native stem cell regeneration may be of use in the fight against ischemic heart diseases. Some minor issues, specified below, are detailed and need to be fixed before publication. The language used in the manuscript is suitable for the topic and only minor, insignificant issues are present. Minor revisions are recommended.

Specific Comments

Introduction:

1. Lines 31-49: The introduction focuses entirely on cardiovascular disease but does not detail the types of myocardial issues and their putative causes. Ischemia from a birth defect that requires surgical repair can cause a different set of lifelong sequelae than ischemia from COPD or other lifestyle-mediated myocardial diseases. It is recommended to make a small table with the type of myocardial damage and potential RBPs/activators of RBPs involved. This will set up the rest of the paper very nicely. Use "unknown" if an RBP activator or other item is not currently reported; such information will also highlight the need for further researches into RBP regulation.

2. Figure 1 is welcome and explains the RBP concept well.

3. What is the role of quality control in the RBP process? There needs to be an initial and general explanation as to the temporal position RBPs take in the post-translational machinery. Do RBPs act before or after folding? Do they assist in folding? Do they participate in the Ub/Prot or autophagy systems? Please make this clear in a few sentences so that the exact utility of RBP regulation as a therapeutic process can be generally localized before the specific RBPs are explained.

Manuscript Body:

1. Of importance: Why were these specific RBPs chosen? Are they myocardium-specific or are they present in other types of cells?

2. Line 133-138: The effect of LIN28A in facilitating hypertrophy in adults vs. regeneration in natal stages needs explanation on the differences. Since the gene/protein itself is not changed, is the sole action of let-7 miRNA the key factor in determining the role of regeneration vs. hypertrophy? Is the oxygen milieu a key determiner of the expression of let-7? And do the Nrf2-mediated antioxidant response or second-messenger reactive oxygen species systems play any role?

3. Line 261-316: This is out of place in a detailed description of individual RBPs. Suggest moving it to the beginning of section 2 as an example process mediated by RBPs to highlight the mechanistic pathways that RBPs are involved in.

4. 2.4, 2.5, 2.6 titles are all in italics, even though, previously, the individual descriptions of RBPs are not. Please be consistent.

5. Table1 is quite welcome and detailed; however, are they listed in some kind of special order? If not, it is suggested to group them based on their roles/positions in mechanistic pathways within the table for ease of reference.

Discussion:

1. The Discussion must mention the role of cardiac stem cells and if Yamanaka (e.g., KLF4), neural crest stem cell factors (e.g., SOX-family factors), or other factors involved in these stem cells also play a role in either regulating RBPs or controlling the outcome of RBP-regulated cardiac myocytes in the differentiation process. The role of c-myc and WNT should also be detailed here…because all developmental biologists will be looking for it.

2. How does exercise regulate RBP expression and activity, especially with respect to cardiac remodeling after ischemia? This needs to be explained, since exercise is a potent regulator of the miRNA that regulate remodeling.

Conclusions:

1. These conclusions are too general. Specific recommendations on RBPs are required to focus future research onto pathways that would be useful in regenerating the myocardium. Which RBPs show the most promise, based on current evidence, of playing a key role in therapeutic development?