

COMMENT

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Heart regeneration is regulated by key micro RNAs from fish to mammals: what it can be learned about the epicardial cells activation during the regeneration in zebrafish

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Zebrafish could be an interesting translational model to understand and improve the post-infarction trial and possible regeneration in mammals. The regenerative capacity in mammalian heart is maintained partially in neonatal life¹ because are still switch-on some phylogenetic-conserved genes; while in adult, it seems to be confined in replacing by a few of cardiomyocytes (CM) and by a large amount of fibroblasts^{2,3}. In contrast, natural cardiac regeneration appears to be excellent in fish after an injury. In zebrafish, the cardiac environment created by cardiomyocytes, fibroblasts, and non-muscle cells after injury is believed to be critical in facilitating the regenerative response⁴. The epicardium-derived cells and the consequent epicardial cells (EPCs) are essential regulators since they respond to FGFs in both embryogenesis and regeneration processes. EPCs undergo to number of cellular modifications^{5,6} that is required to be silenced by miRs that controlled the differentiation of the cells. This downregulation is a necessary event to activate the transition from epithelial to mesenchymal cells, such as cytoskeletal re-arrange and expression of hyaluronan-mediated motility receptor, necessary to move in the damage site^{7,8}. In the heart several molecules are involved in the protein synthesis regulation⁹ where the miRs have an upstream action. miR1 and miR133 (a and b) are involved in the activation of fibroblasts in producing FGFs^{10,11}, as well as the hypertrophic response of epithelial and muscular cells after injury, to compensate for

the loss-of-contractile tissue in mammals, as well as in zebrafish^{9,12–14}.

In the recent research edited in *Cell Death and Discovery*¹⁵, we have explored the time lapse of downregulation of miRs 133a, 133b, and miR1 during the regeneration trial in zebrafish, discovering that the downregulation occurs already after 24 h post injury (hpi) and had become critical during the next 48 hpi (Fig. 1). Moreover, by using laser microdissector method we have demonstrated that this downregulation occurs differently in activated EPCs as compared to the site of regeneration. Next to the evaluation of miRs expression, we have analysed the expression of embryonal molecules that are re-expressed during the regeneration process: Wilms' Tumor factor 1 (WT1, that is a marker for activated EPCs cells); Heat Shock Protein 70 (HSP70, a chaperon molecule activated during the embryogenesis in a double function: block the apoptosis and help in the folding/transport of neo-synthesized proteins) and one of the cardiac Troponin complex (cTNT, factor T, is the molecule that adheres to the tropomyosin and is determinant for the correct contraction of the muscle cardiac fibers, it is early expressed and indirectly controlled by miR1). It is probable that the block of myogenic or hyperplastic role of miR1 is crucial in activating the regeneration process. miR133a is probably a key miR that can activate the epicardium because it showed a more significant downregulation already at 1 dpa. Again, the miR133b could be a key miR because of its direct control on the CTGF protein, necessary to regulate the transition in endocardial cells from epithelial to mesenchymal elements. The Fig. 1 gives a synthesis of the

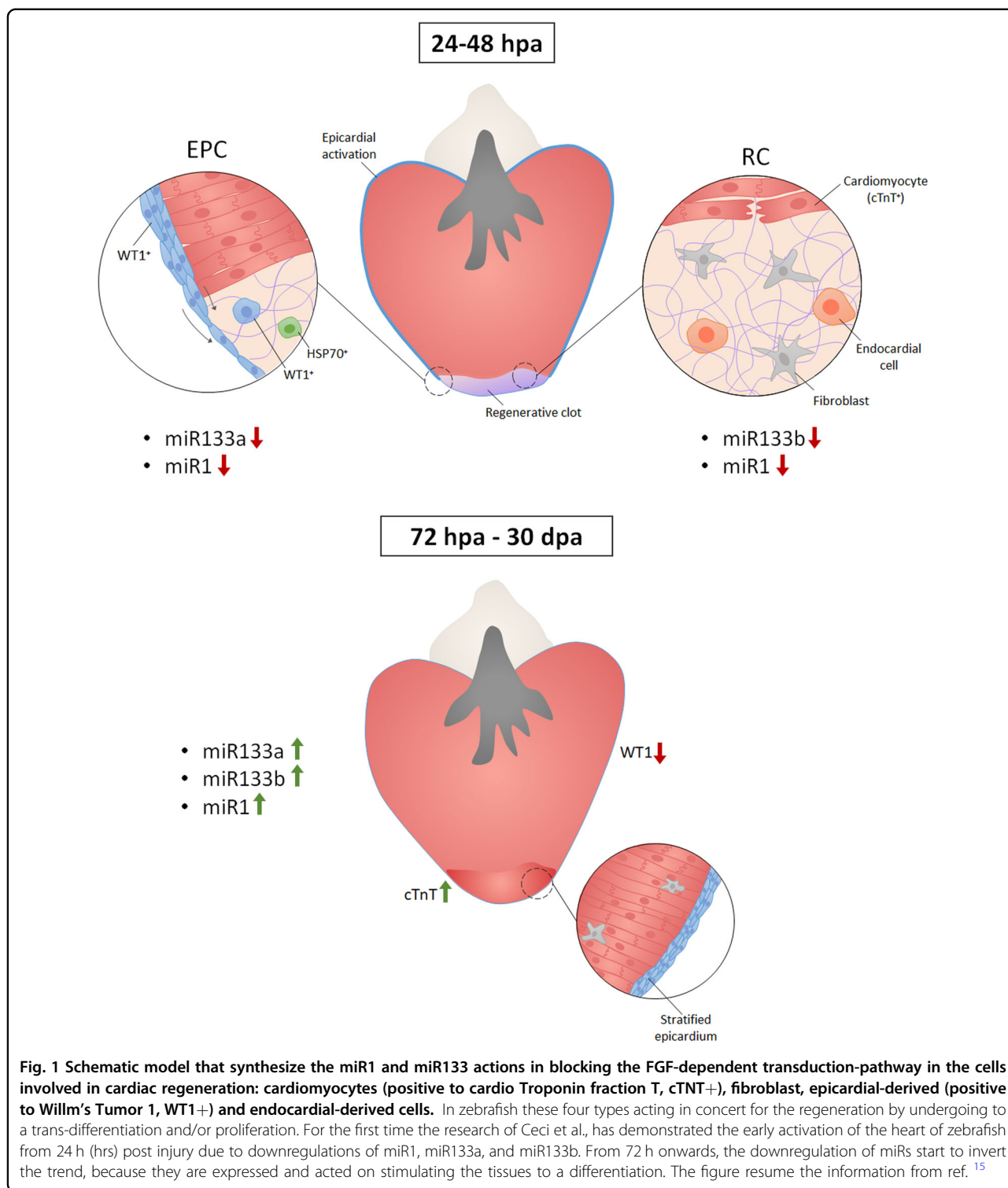
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cited article and details are available in Ceci et al.¹⁵. This study provides key clues for the experimental early activation of pro-regenerative responses in the heart in zebrafish, and provides crucial insights for the development of therapies targeting heart disease.

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Conflict of interest

The authors declare that they have no conflict of interest.

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