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Researchers defined the early lineage segregation during early mammalian heart development

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The heart contains four different chambers and different cell types such as cardiomyocytes (CMs), endocardial cells (ECs) covering the inner layer of the heart, epicardial cells covering the outer layer of the heart and smooth muscle cells (SMCs) covering the coronary arteries and main vessels. During embryonic development, the cells that will formed the heart need to be specified at the correct time, migrate at the correct place, proliferate to ensure the harmonious morphogenesis and growth of the heart. Any defects during this critical stage of development will lead to congenital heart diseases, which represent the first cause of severe birth malformations. While different progenitors that contribute to the development of the heart have been identified, it remains unclear whether these cells arise from common progenitors or derive from distinct progenitors that are specified at different time during development.

In a new study published in *Nature Cell Biology*, researchers led by Pr. Cédric Blanpain, MD/PhD, WELBIO investigator at the IRIBHM, Université libre de Bruxelles, Belgium, have identified temporally distinct populations of cardiac progenitors that differentiate into different cell lineages and contribute to different regions of the heart.

Fabienne Lescroart, Samira Chabab and colleagues performed for the first time a temporally controlled clonal analysis of early cardiac progenitors, in which they marked single cells at the early stages of

embryonic development and assess the contribution of single cardiac progenitors to the heart development. In contrast to the prevalent notion that these cells arise from a common progenitors, the researchers found that the different cardiac progenitors are specified at different time points during development and will only contribute to the morphogenesis of certain cardiac regions, like if the heart is build from different blocs that are made at different time during development. Furthermore, the researchers found that in contrast to the multilineage differentiation of these cells in vitro, the early population of cardiac progenitors did not differentiate into all cardiovascular lineages in vivo, but were rather pre-specified to give rise to either cardiac cells or endocardial cells, suggesting that the ultimate fate of the progenitors can be regulated by the environmental cues that the different progenitors encounter during cardiac morphogenesis. "We were extremely surprized to find that the early the cardiac progenitors have a much narrow regional contribution and were not able to differentiate into more than one cell types in contrast to late born cardiac progenitors. We need to completely rethink about the way heart is formed" comment Fabienne Lescroart, the first author of the study.

Using new tools to isolate for the first time the early cardiac progenitors during embryonic development, Fabienne Lescroart, Samira Chabab and colleagues define the molecular characteristics of these different progenitors and showed that the different populations of Mesp1 progenitors, although very similar molecularly, present also notable difference, consistent with their lineage and regional contribution. In addition, characterization of the gene expression at a single cell level have shown that the cardiac progenitors were molecularly heterogenous and expressed different combination of genes that will define the cell fate and regionalization of each progenitors. Understanding how this specificity is achieved will be important to instruct and/or restrict the fate of multipotent cardiovascular progenitors into a particular cell lineage in vivo. The answers to these questions will be important to

design new strategies to direct the differentiation of pluripotent cells and iPS cells specifically into pure population of cardiac cells, and for improving cellular therapy in cardiac diseases.

In conclusion, this work uncovers how the heart is build from temporally distinct progenitors with different differentiation potential. This work provides the first temporal clonal analysis of heart development and the first molecular characterization of cardiac progenitors at the early step of cardiac morphogenesis. " This new study really changes the way we think about cardiac development and have important implications for better understanding the aetology of congenital cardiac malformations and should be the starting point of further studies to understand how the regionalization and the choice of differentiation into a particular cardiovascular lineage is achieved, which have important implications for improving cell therapy during cardiac repair" comments Pr Cédric Blanpain, the senior author of this study.

More information: Fabienne Lescroart , et al. "Early lineage restriction in temporally distinct populations of Mesp1 progenitors during mammalian heart development." *Nature Cell Biology* 2014, DOI: 10.1038/ncb3024