Title: Myocardial infarction ´through the window´: dual dynamics for cardiac fibroblasts activation

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Abstract (250 words).

Activated cardiac fibroblasts (CFs) are responsible for the healing of the heart tissue after a myocardial infarction (MI). Based on high throughput technologies, several groups have recently demonstrated their heterogeneity and a unique role of each subpopulation of CFs during the ventricular remodelling process. This is relevant towards the discovery of personalized treatments to control the initial post-MI healing scar that will contribute to preserve ventricular function and prevent the onset of heart failure. However, little is known about the moment that CFs are activated, and which genes are potentially involved in this process. Using a mouse model for MI and single cell RNA-Seq, we demonstrate that the activation of Reparative Cardiac Fibroblasts (RCFs), the CFs responsible for the healing scar, happens within the first week after MI. Interestingly, our data reveals that all CFs show high expression of the top markers genes for RCF in a specific moment, but only few of them finally evolve to an RCF transcriptomic

identity. Furthermore, we describe two different molecular dynamics that could give rise to this activation and, in consequence, the appearance of definitive RCFs. Using Spatial Transcriptomics, we localized the genes related to each dynamic in different anatomical regions of the infarcted heart, but, remarkably, only one persists seven days after MI. These results highlight the existence of a specific “window of activation” of RCFs at the beginning of the ventricular remodelling process. This potential ´therapeutical window´ could allow us to regulate the size of the healing scar and, in consequence, the poor prognosis for patients that have suffered an ischemic event.