



1. DATOS BÁSICOS DEL TFG:

Título: Single-cell RNA Sequencing Dissection of Endothelial-to-Mesenchymal Transition and Autophagy Dysregulation in Atherosclerosis

Descripción general (resumen y metodología):

Atherosclerosis, a chronic inflammatory disease of arterial walls, is the leading cause of cardiovascular disease (CVD). Its pathophysiology involves endothelial activation, monocyte recruitment, smooth muscle migration, macrophage and foam cell involvement, and extracellular matrix instability. Endothelial-to-mesenchymal transition (EndoMT) has recently emerged as a key driver of vascular inflammation in atherosclerosis, marked by endothelial cells partially losing their identity and acquiring mesenchymal traits. This transition disrupts cell junctions, increases permeability, and perpetuates inflammation, fueling disease progression. While endothelial dysfunction initiates atherosclerosis, autophagy — a cellular recycling process — also plays a crucial role in plaque development. Understanding the mechanisms linking EndoMT and endothelial autophagy could offer important clinical insights. This project aims to characterize the cellular heterogeneity and molecular signatures of EndoMT in atherosclerotic plaques by applying scRNA-seq on mouse models of atherosclerosis and human carotid endarterectomy samples. Special focus will be placed on identifying the transcriptional programs involved in partial EndoMT, autophagy regulation, and plaque instability.

Tipología: Estudio de casos, teóricos o prácticos, relacionados con la temática del Grado.

Objetivos planteados:

Map endothelial cell populations undergoing EndoMT in murine and human atherosclerotic lesions at single-cell resolution. Identify gene expression profiles associated with autophagy-related pathways during EndoMT. Compare conserved and divergent EndoMT-associated transcriptional programs between mice and humans. Validate key molecular regulators of EndoMT-autophagy interplay using spatial transcriptomics and immunostaining.

Bibliografía básica:

1- Wirka RC, Wagh D, Paik DT, et al. (2019). Atheroprotective roles of smooth muscle cell phenotypic modulation and the TCF21 disease gene as revealed by single-cell analysis. *Nature Medicine*, 25(8):1280-1289. This paper demonstrates the application of scRNA-seq to identify distinct cellular phenotypes in atherosclerotic plaques. 2- Pan H, Xue C, Auerbach BJ, et al. (2020). Single-Cell Genomics Reveals a Novel Cell State During Smooth Muscle Cell Phenotypic Switching and Potential Therapeutic Targets for Atherosclerosis. *Circulation Research*, 126(11):1472-1487. Showcases how scRNA-seq can identify novel cell states and transition processes in atherosclerosis. 3- Evrard SM, Lecce L, Michelis KC, et al. (2016). Endothelial to mesenchymal transition is common in atherosclerotic lesions and is associated with plaque instability. *Nature Communications*, 7:11853. Foundational paper establishing the importance of EndMT in atherosclerotic plaque progression. 4- Grootaert MOJ, Roth L, Schrijvers DM, et al. (2018). Defective autophagy in atherosclerosis: To die or to senesce? *Oxidative Medicine and Cellular Longevity*, 2018:7687083. Comprehensive review on the role of autophagy dysfunction in atherosclerotic disease progression. 5- Sergin I, Evans TD, Zhang X, et al. (2017). Exploiting macrophage autophagy-lysosomal biogenesis as a therapy for atherosclerosis. *Nature Communications*, 8:15750. Explores the therapeutic potential of targeting autophagy pathways in atherosclerosis. 6- Dai Y, Xu M, Wang Y, et al. (2023). Impaired autophagy contributes to endothelial-to-mesenchymal transition in

atherosclerosis progression. Molecular Medicine Reports, 27(2):30. A recent paper connecting autophagy dysfunction with EndMT in atherosclerotic progression

Recomendaciones y orientaciones para el estudiante:

Plazas: 1

2. DATOS DEL TUTOR/A:

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