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1. Title:

Development of a 3D model of granulomatous vasculitis: a research tool for investigating immunopathogenic mechanisms of granulomatosis with polyangiitis.

2. Scientific abstract:

Systemic vasculitides encompass a heterogeneous group of chronic inflammatory diseases characterized by inflammation of blood vessels, which results in the occlusion, dilatation or rupture of the involved vasculature. Vasculitis are serious diseases, with an overall mortality of 15-20% and the potential of deeply impairing the quality of life of affected individuals. However, ethiopathogenesis of vasculitides remains poorly understood. Granulomatosis with polyangiitis (GPA) is a primary autoimmune vasculitis characterized by granulomatous inflammation in addition to smaill-vessel necrotizing vasculitis. Granulomas consist of compact accumulations of activated lymphocytes and macrophages, usually with formation of multinucleated giant-cells with tissue-injuring capacity. Mechanisms leading to granulomatous lesions in GPA are virtually unknown. Understanding the molecular mechanisms underlying early granuloma formation, cross-talk between cell subtypes, i.e., lymphocytes and macrophages, or influence of the microenvironment, i.e., stromal cells, extracellular matrix, endothelial cells, may lead to the identification of new therapeutic targets. To better recapitulate the biology and 3D architecture of human systems in these inflammatory diseases, we propose the development of 3D multi-cellular cultures where patient-derived cells can be used to develop granulomatous inflammation. The current proposal is aimed to investigate major pathogenic events responsible for the development and progression of GPA granulomatous inflammation, their modulation by new therapeutic agents in state-of-the-art new 3D systems, and translation of discoveries to optimize patient's health.

3. Keywords: *anca, vasculitis, 3D models, granulomatosis with polyangiitis, inflammation.*