DEC 7th 2020 | 4PM CET VIRTUAL

iPSZÜRICH

A Lecture Series Focused on Induced Pluripotent Stem Cells

funded by a GRC Grant, UZH

Roche

Florian Wanke, PhD
Inflammation and Immunology Discovery, Roche Basel, Switzerland

USING iPSC-DERIVED "TISSUE-RESIDENT" MACROPHAGES FOR DRUG DISCOVERY

Tissue-resident macrophages are key players in inflammatory processes but also crucial for tissue homeostasis and repair. Due to their important role, dysregulation of macrophages has been implicated in several diseases including autoimmunity and cancer. Therefore, macrophages are a prime target for drug discovery. Currently, the main sources of macrophages used for therapeutic compound screening are primary cells isolated from blood or tissue or immortalized or neoplastic cell lines (e.g., THP-1). We have recently described an improved method to employ human induced pluripotent stem cells (iPSCs) enabling efficient, large-scale production of cells resembling tissue-resident macrophages. Transcriptome analysis of iPSC-derived macrophages revealed a similar expression pattern of key signature genes compared to monocyte-derived macrophages. Moreover, they exhibited key functional characteristics of primary macrophages such as cytokine release, phagocytosis and chemotaxis. Interestingly, we found receptors involved in clearance of apoptotic cells, a process termed efferocytosis, to be significantly elevated in iPSC-derived macrophages. Particularly, members of the TAM family of receptor tyrosine kinases (TAM RTKs) were higher expressed on iPSC-derived macrophages which displayed an increased efferocytic capacity compared to monocyte-derived macrophages. Using this cellular model we found stimulation with the natural TAM RTK agonist GAS6 to significantly enhance the uptake of apoptotic cells which was dependent on MERTK expression. Our results highlight the use of iPSC-derived macrophages as a representative cellular model to study key functionalities of tissue-resident macrophages. Furthermore, large-scale production of these cells overcomes previous limitations and enables high-throughput screening of compound libraries.