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PPARγ, a major actor of bone marrow stroma homeostasis and a myelofibrosis therapeutic target ?

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Myelofibrosis (MF) is a rare myeloproliferative neoplasia (MPN) with very few therapeutic options, in which hematopoietic malignant cells affects bone marrow microenvironment's structure, composition and function through an inflammatory context. We previously reported that treatment of MF preclinical models with PPARγ pharmacological agonists was able to counteract major axis of the pathology by reducing myeloproliferation, inflammation, fibrosis and osteosclerosis.

To decipher the function of PPARγ in bone marrow mesenchymal stromal cells (MSC), we studied its transcriptomic expression in MSC (GEO2R database). We found a downregulation of PPARγ expression in MSC from MF patients and murine MF models but not in MPN without fibrosis. In order to mimic this observation and characterize PPARγ's role in MSC, fibrosis, osteosclerosis and hematopoietic support, we designed an *in vitro* model of PPARγ knock out in MS-5, a MSC cell line.

First, we found that PPARγ knock out impacts MSC's fate by inhibiting their adipocyte differentiation in favour of an enhanced RUNX2-mediated osteo-chondrocyte differentiation. Accordingly, the secretion of adipocyte factors is reduced and we observed an increased secretion of osteoprotegerin (OPG) which acts as a decoy receptor for RANK-L and impairs osteoclast differentiation and survival. This key role of PPARγ in both enhanced bone production and reduced bone resorption may explain MF-associated osteosclerosis and its reduction after PPARγ agonists' treatment.

On the marrow axis, our *in vitro* MSC model shows an increased expression of a panel of pro-fibrotic TGFβ-induced gene that recapitulate observations we made in MSC from MF patients and murine MF model (GEO2R). Among these genes, a dramatic increased expression of Acta2 suggest a switch from mesenchymal stromal cells to myofibroblast, a fibrosis-associated cell type.

From an hematopoietic aspect, PPARγ knock out MSC shows an important decrease of SCF expression and secretion associated with a strong loss of ability to support short and long-term hematopoiesis. Furthermore, we also found a strong decrease of CXCL12 and VCAM1 expression and secretion, which may be responsible for progenitors/HSC retention impairment in bone marrow during MF.

This PPARγ invalidation model in MSC mimics the bone marrow remodelling observed in MF, at the same time in terms of fibrosis, osteosclerosis and hematopoietic support and highlights the therapeutic target position of PPARγ in MF.