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Myeloproliferative disorders

DISSECTING THE ROLE OF CCL2/CCR2 AXIS IN MYELOFIBROSIS: TRANSLATIONAL EVIDENCE FROM MURINE MODELS TO HUMAN CELLS

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Introduction: Dysregulated inflammatory signalling is a key feature of myeloproliferative neoplasms, most notably of myelofibrosis (MF). Recent studies have pinpointed the mechanistic relevance of cytokine/receptor axes. Our research group is currently investigating the role of the CCL2/CCR2 axis in a mouse model of MF, the GATA1low mice, and in primary patient cells, to identify a novel biomarker and potential druggable target.

Methods: We investigated CCR2 expression by immunohistochemistry (IHC), and immunofluorescence (IF) in bone marrow (BM) and spleen specimens from GATA1low mice, whose phenotype recapitulates key pathological features of the human disease: megakaryocytic (MK) hyperplasia, BM fibrosis, and extramedullary hematopoiesis. Moreover, CCR2 and GATA1 expression was evaluated in BM biopsies, PB/BM isolated CD34pos cells, and ex vivo-derived MKs from MF patients.

Results: The BM and spleen of GATA1low mice presented a profoundly disrupted morphological architecture, with massive infiltration of atypical immature CCR2pos MKs, some of which displayed unexpected nuclear positivity. IF studies identified different MK populations with variable CCR2 expression: mature CCR2neg MKs and immature, dysmorphic MKs staining positive for CCR2, also in the nucleus. Samples from control mice were negative for CCR2pos cells. MF bone marrow biopsies revealed a diffuse infiltrate of CCR2pos cells, staining positive also for c-KIT. Consistent with the mouse model, human MF BM displayed heterogeneous MK populations, with immature, aberrant CCR2pos MKs. CD34-pos cells isolated from MF patients displayed increased CCR2 expression as compared to healthy donors, paralleling the degree of BM fibrosis. Interestingly, CD34pos cells showed mutually exclusive CCR2/GATA1 expression: MF CD34pos cells were CCR2pos /GATA1neg, while normal CD34pos cells were CCR2neg/GATA1pos. During in vitro MK differentiation, MF CD34pos cells showed reduced differentiation capacity compared to healthy donors and produced immature CD41low and CD61low MKs that were highly positive for CCR2. Of note, ex vivo-derived MKs displayed a similar mutually exclusive pattern of expression of CCR2 and GATA1.

Conclusions: Our findings support a model in which the neoplastic clone in MF aberrantly expresses CCR2 in a GATA1–dependent manner, suggesting that the CCL2/CCR2 axis may contribute to MK dysfunction and fibrotic progression in MF. Targeting this axis could offer novel insights into MF pathophysiology and therapeutic strategies.