CD8+ T cells, reinforcing immune immaturity. Frequencies of mature and cytotoxic NK cells (CD56dim, CD57+, NKp80), as well as NKG2D and DNAM-1, were lower in DX, F, and TFRL groups compared to DMR100, TFR, and healthy controls. PD-1 and CTLA-4 expression on CD8+ T cells was more pronounced in these groups. No significant differences were found in KIR2DL1 and NKG2A on NK cells or CD3, CD4, CD8 expression on T cells. **Discussion and conclusion:** These findings suggest that maturation and activation of cytotoxic compartments are crucial for disease control and TFR success. In contrast, immature and exhausted immune profiles may predispose to relapse. Immune dysregulation precedes molecular relapse, reinforcing the role of longitudinal immune monitoring. Progressive loss of mature NK cells and increased checkpoint expression may define an immunological risk profile for TFR failure. Immune assessment during dose reduction could guide clinical decisions on TKI cessation and support individualized strategies in CML based on immunological profiles.

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IMMUNE SENESCENCE AND EXHAUSTION PHENOTYPE MARKED BY LOSS OF NKG2D AND DNAM-1 NK ACTIVATING SIGNALING AND INCREASED TIM-3 T CD8 CHARACTERIZES ADVANCED MYELOFIBROSIS

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Introduction: Myelofibrosis (MF), driven by JAK/STAT signaling mutations in hematopoietic stem cells, has the worst prognosis among myeloproliferative neoplasms (MPNs), progressing from pre-fibrotic MF (PFMF) to overt MF (OMF). Although additional mutations promote clonal expansion, progression cannot be fully explained by clinical- mutational scores. Exposure to the leukemic inflammatory microenvironment may impair immune surveillance by cytotoxic cells such as Natural Killer (NK) and T lymphocytes, fostering disease advancement. **Objectives:** To investigate immune dysfunction across clinical and molecular MF subtypes, focusing on NK and T lymphocyte phenotype, maturation, and receptor expression, and to examine the leukemic microenvironment effects using a JAK2V617F murine model. **Material and methods:** We performed immunophenotyping of NK and T cells (frequency, maturation, and activation/inhibitory receptors) in peripheral blood mononuclear cells from untreated MF patients (13 PFMF, 16 OMF; 13 JAK2 wild-type, 18 JAK2-mutated) admitted at Ribeirao Preto Clinical Hospital (August 2022 – December 2024), and from age-matched healthy donors. To further explore the effects of soluble factors from the leukemic microenvironment, we established a chimeric murine model of JAK2V617F- driven MPN. Healthy recipient mice were transplanted with total bone marrow from JAK2V617F donor mice following sublethal irradiation (n = 4 MPN-exposed, 6 control- exposed). Four weeks post-transplant, spleen cells were collected, and NK and T cells were immunophenotyped. **Results:** MF patients exhibited increased frequencies of NK cells (CD45hiCD3-CD19-CD56+) compared to healthy donors, particularly CD56bright and immature subsets (CD27-CD11b-, CD27+CD11b-), and reduced frequencies of CD56dim, cytotoxic (CD27-CD11b+), and hypermature (CD57+NKp80+) NK cells. There was a decrease of NKG2A (total, cytotoxic, and hypermature NK cells) and NKp46 (total and hypermature NK cells) receptors. T cell maturation was also impaired, with reduced frequencies of stem central memory (CD45RO-CCR7+CD62L+CD27+CD45RA+) and central memory (TCM: CD45RO+CCR7+CD62L+CD27+CD45RA-) subsets in CD4 cells, and TCM in CD8 cells. Terminally differentiated effector memory (CD45RO-CCR7-CD62L-CD45RA+) cells increased in both lineages. CD8 T cells also showed decreased NKG2D expression. During disease progression from PFMF to OMF, there was a further increase in hypermature NK cells and downregulation of DNAM-1 and NKG2A. JAK2-mutated patients showed decreased expression of KIR2DL1 (total and hypermature NK), reduced CD4 T cells, increased CD8 T cells, and decreased CD8 TCM cells. The MPN-exposed group exhibited reduced frequencies of mature NK cells (CD45hiCD19-CD3-CD122+NK1.1+CD49b+NKp46+), NKG2D expression, and T cell frequencies (CD45hiCD19- NK1.1-CD3+), but increased CD8 T cells, with elevated TIM-3 expression.

Discussion and conclusion: These findings reveal distinct immune signatures associated with MF progression and JAK2V617F. NK cell dysfunction, characterized by impaired maturation and loss of activating receptors, may compromise immune surveillance and promote leukemic transformation. Concurrently, T cell alterations suggest chronic inflammation and immunesenescence, particularly in JAK2-mutated cases. The murine model supports a direct role for JAK2V617F-mutant hematopoiesis in driving immune exhaustion. Collectively, our data highlights the contribution of immune dysfunction to MF pathogenesis and progression, providing insights into how molecular heterogeneity may influence disease.

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IMPACT OF ABCB1 AND ABCG2 POLYMORPHISMS ON TROUGH IMATINIB CONCENTRATION IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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