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POSTER ABSTRACTS

509.BONE MARROW FAILURE AND CANCER PREDISPOSITION SYNDROMES: CONGENITAL

Immune Signature in Telomere-Biology Disorders

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Excessive telomere shortening caused by pathogenic germline variants in telomere-biology genes may result in bone marrow failure, hematopoietic malignancy and extramedullary complications, such as idiopathic pulmonary fibrosis (IPF), liver cirrhosis, and solid tumors. Patients with short telomeres also may develop immunodeficiency with low counts of T-cell receptor excision circles (TRECs), kappa-deleting excision circles (KRECs), and CD4 $^{+}$ T cells. The aim of the present study was to comprehensively determine the immune system changes in human patients with telomeropathies by deep-phenotyping peripheral blood mononuclear cells (PBMCs) and quantifying cytokine serum levels. We applied a 39-marker panel of metal-labeled antibodies and employed mass cytometry (CyTOF) to assess the subsets of lymphocytes, monocytes, and dendritic cells (DC) in 20 patients and 10 healthy individuals. High-dimensional analysis was conducted using automated clustering (*Flow-SOM*) to identify subpopulations and cell states, whereas *t-SNE* was employed as a visualization tool. A total of 32 serum cytokines, chemokines and growth factors were quantified by a bead-based immunoassay (Luminex^{TM}). First, we confirmed previous findings of low CD4/CD8 ratio (0.73±0.56 vs. 1.3±0.69 in controls, p=0.05), and reduced absolute naïve (CD45RA $^{+}$CCR7 $^{+}$) CD4 $^{+}$ and CD8 $^{+}$ cell counts (p<0.01), with effector memory cell accumulation in patients with telomere diseases, and the current study further showed a reduction in naïve B (CD19 $^{+}$IgD $^{+}$CD27 $^{-}$) and in recent thymic emigrants (RTE), characterized by CD31 $^{+}$CD45RA $^{+}$ (p<0.01), indicating a consistent aged B and T cell profile. T $_{H}$1, T $_{H}$17 and T $_{H}$17.1 CD4 $^{+}$ lymphocytes were reduced (p<0.05), whereas the T $_{H}$2/T $_{H}$1 ratio was increased (1.6±0.83 vs. 0.82±0.39 in controls; p=0.013), demonstrating a dysregulated T helper cell diversity. T $_{regs}$, on the other hand, did not appear to be affected. Plasmacytoid DCs (CD3 $^{-}$CD141 $^{+}$CD123 $^{+}$CD1c $^{-}$), which are known inducers of T helper differentiation, were reduced in patients (p=0.014). A double negative T cell (DNT) population, characterized as CD3 $^{+}$CD4 $^{-}$CD8 $^{-}$Vd2 $^{-}$Tbet $^{+}$Granzyme B $^{+}$, was significantly increased (p=0.0002). Activated effector memory and TEMRA CD4 $^{+}$ cells, also expressing exhaustion markers PD-1 and TIGIT (CD4 $^{+}$CD45RA $^{+/-}$CCR7 $^{-}$CD38 $^{+}$HLADR $^{+}$Ki67 $^{+}$PD-1 $^{+}$TIGIT ^{low}) and proliferating switched memory B cells (CD3 $^{-}$CD19 $^{+}$IgD $^{-}$CD27 $^{+}$Ki67 $^{+}$) were higher (p=0.046 and p=0.041, respectively) suggesting the occurrence of an environment prone to immune activation, also supported by the prevalence of CD14 $^{+}$CD16 $^{+}$CXCR3 $^{+}$CCR4 $^{+}$ classical monocytes (p=0.0042). Additionally, mucosal-associated invariant T (MAIT) cells (CD3 $^{+}$CD161 ^{high}Vα7.2 $^{+}$) were markedly reduced in patients (p<0.0001), possibly due to their recruitment to other tissues as a response to inflammation. Conversely, immature NK cells (CD3 $^{-}$CD19 $^{-}$CD56 ^{bright}CD16 $^{-}$) were more frequent in patients as compared to controls (p=0.026), and individuals with the shortest telomere lengths had an even higher frequency of these cells. In addition to the previously described CD4 $^{+}$ immunodeficiency, the predominance of immature NK cells may potentially impact the immunosurveillance of malignant transformations. When an unsupervised clustering algorithm using cell subpopulations as variables was applied, patients and controls were correctly identified in 100% of cases. Telomere length positively correlated with some cytokine levels in serum. This was observed for angiopoietin-1, IL-1 superfamily, IL-3, IL-4, IL-7, IL-23, IL-27, M-CSF, MCP-1, MIP-3a and PDGF-BB. Taken together, our results reveal a distinct immunophenotype in telomeropathies, which comprises deficient or skewed maturation of certain subsets, an aged phenotype of B and T cells, aberrant lymphocyte activation and very low levels of circulating MAIT cells, which might be indicators of ongoing inflammatory processes, tied with dysregulated cytokine levels. This immune perturbance may contribute to the clinical onset of telomeropathies and increase the risk of infections, cirrhosis, IPF and cancer development.

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Disclosures No relevant conflicts of interest to declare.

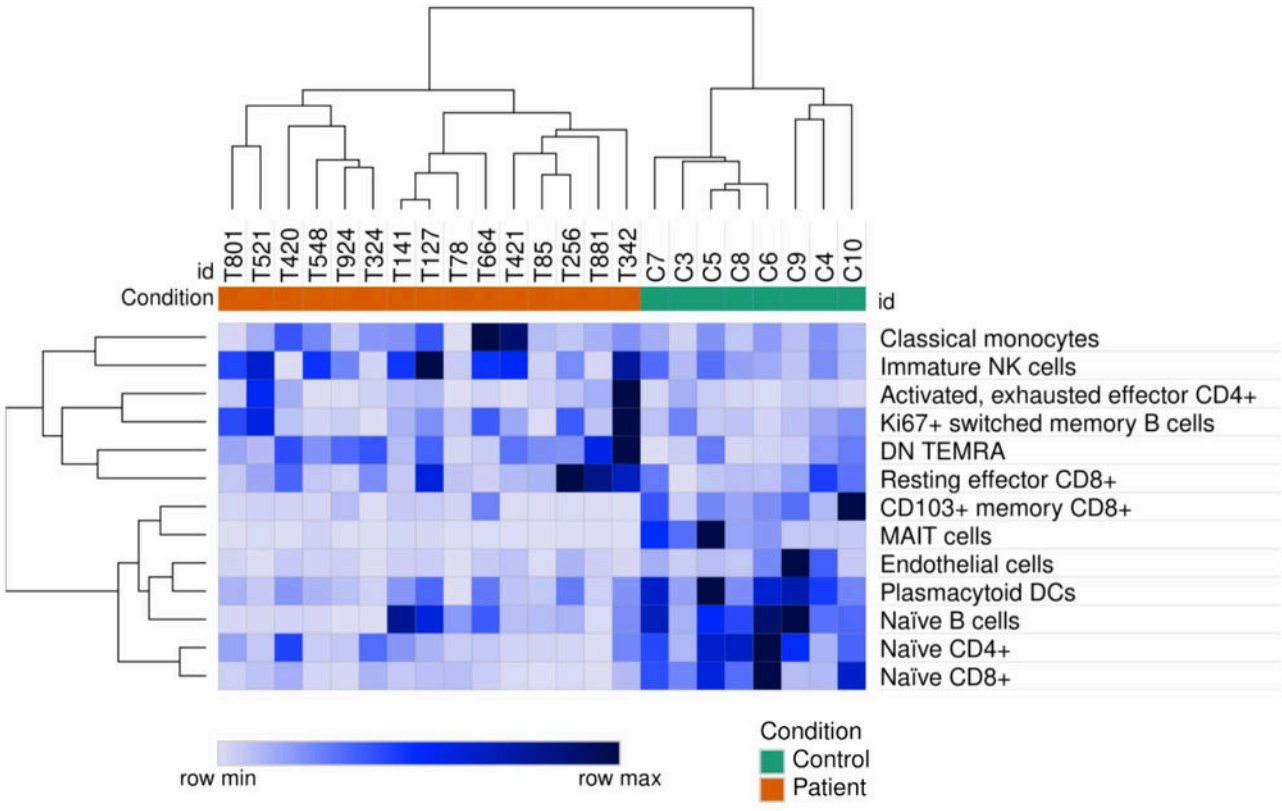

Figure 1. Unsupervised clustering of TBD patients and healthy controls by significantly different cell subpopulations.

Figure 1

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