Acquired Aplastic Anemia Shows Increased Nestin+ Niche Numbers, Upregulation of Genes of the Adaptive Immune System Cells and of CXCL12 in Transformation

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Introduction

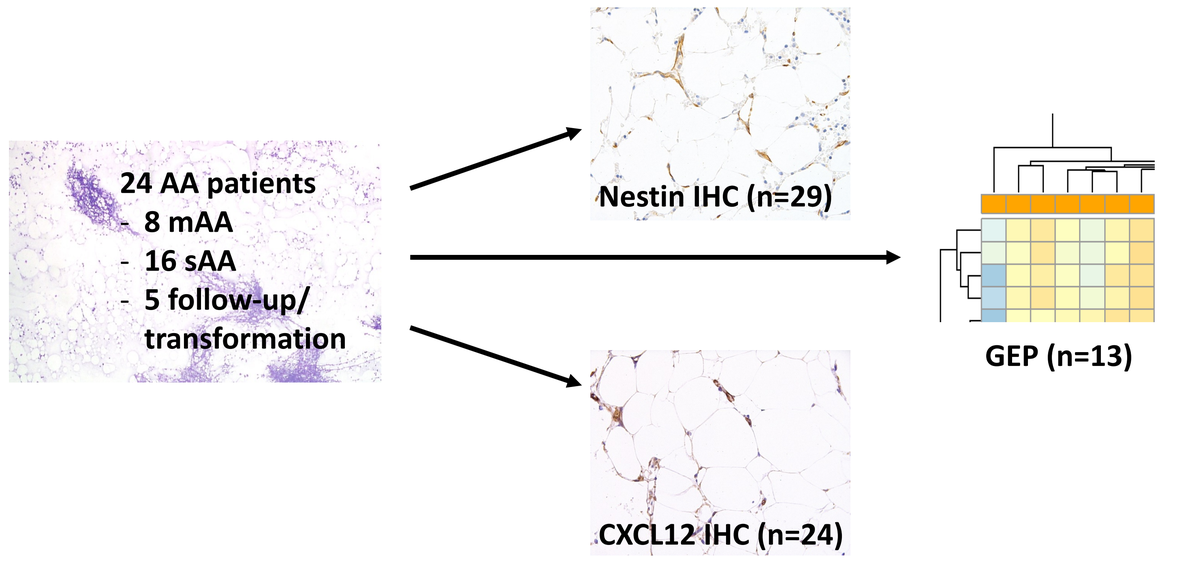
Acquired aplastic anemia (AA) is characterized by severe cytopenia usually due to an immune-mediated destruction of the hematopoietic stem cells (HSC). The influence of the HSC niche in the disease pathogenesis is not well understood

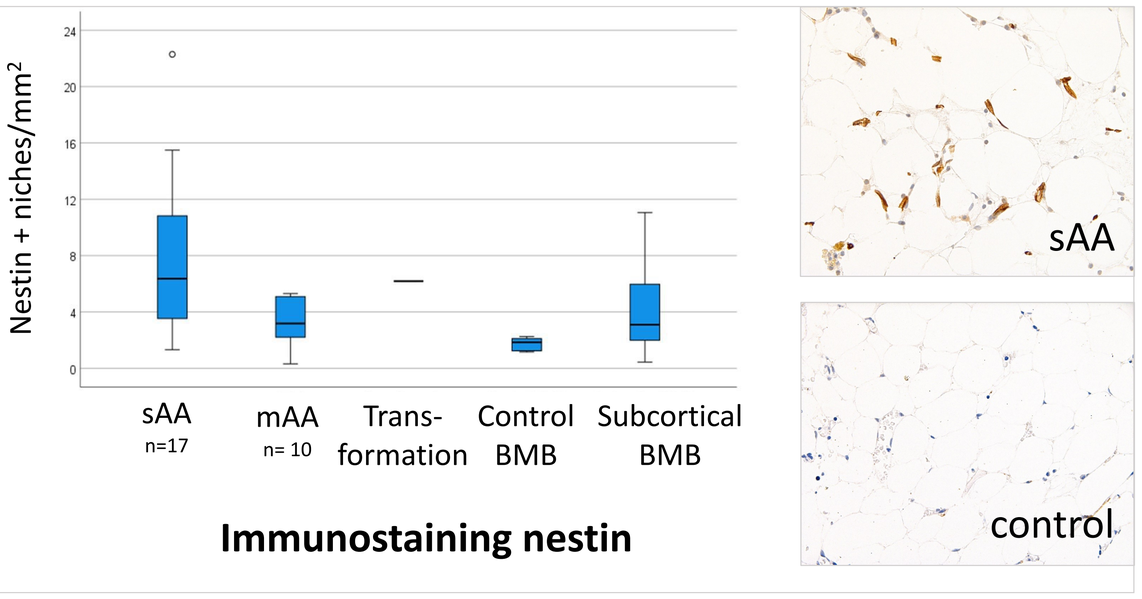
Nestin+ niches
- important role in the healthy bone marrow (BM)
- dysregulation: MPN, AML and GvHD

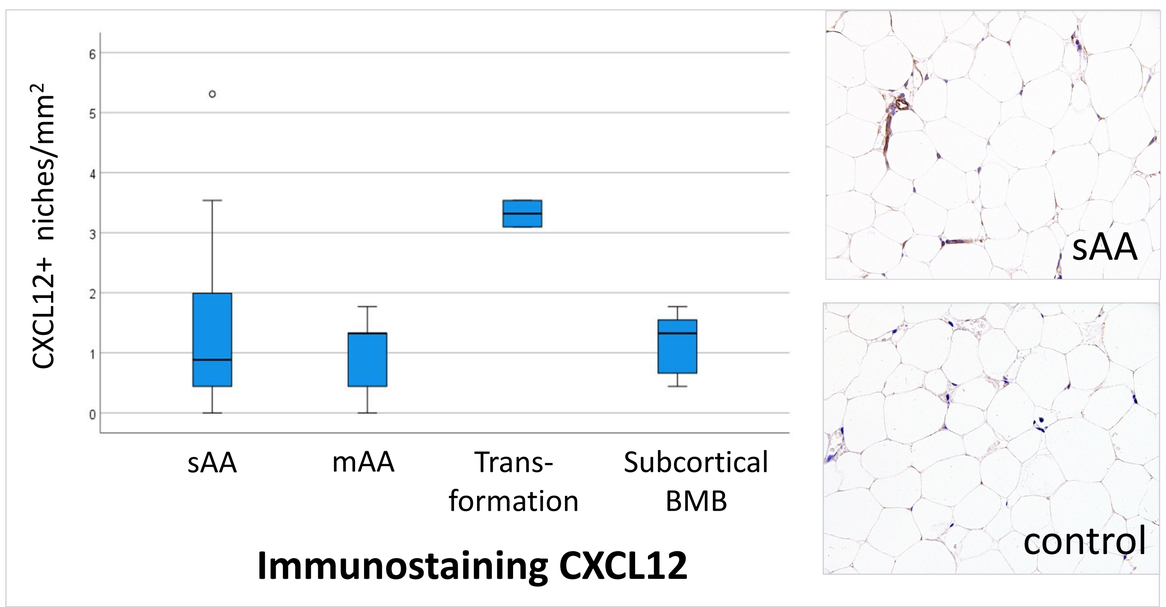
CXCL12
- involved in maintenance & circadian rhythmicity of hematopoiesis
- adhesion & survival of hematopoietic cells and malignant clones

Methods

- Immunohistochemical (IHC) stainings for nestin and CXCL12:
  - 29 bone marrow biospies (BMB) of 24 patients with moderate (mAA) and severe AA (sAA)
  - 12 control normal BMB samples obtained along staging procedures or from healthy BM donors
  - 7 control BMB from physiologically hypocellular subcortical spaces to exclude the influence of cellularity
- Gene expression profiling (GEP):
  - 13 AA cases and 4 controls utilizing the HTG Transcriptome Panel®
- Biomedical modelling

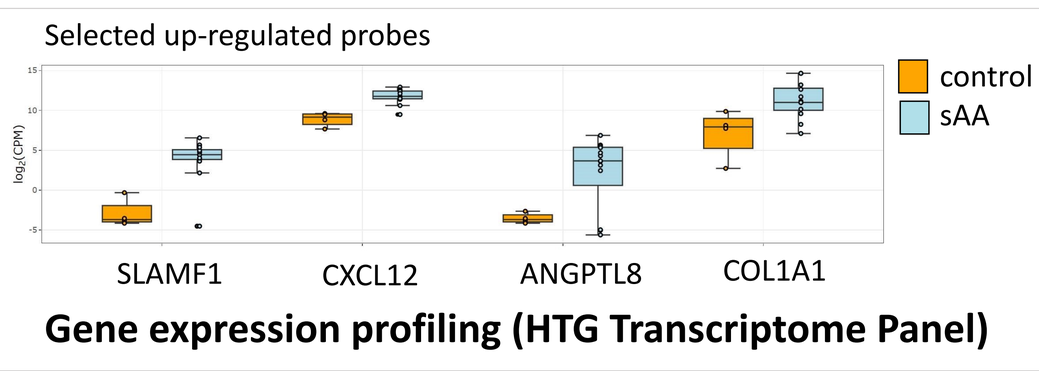






Results

- **Nestin⁺ niches are increased in patients with sAA** (mean 7.8 niches/mm²) compared to mAA (mean 3.3/mm²), normal BM (mean 1.7/mm2) and physiologically hypocellular subcortical BM spaces (mean 4.4/mm²; $p^{Kruskal\ Wallis}<0.001$).
- **CXCL12⁺ niches do not differ** between patients with mAA (mean 1.3 niches/mm²), sAA (mean 1.5/mm²) and physiologically hypocellular subcortical BM spaces (mean 1.1 niches/mm²), but are increased in the two samples of patients who transformed to myeloid malignancies (mean 3.3/mm²).
- GEP shows considerable **upregulation of *SLAMF1, CXCL12, ANGPTL8, CTNNB1, COL1A1* and *PECAM1***.
- Biomedical modelling reveals a **gene expression signature of the adaptive immune system in SAA** (CD4⁺ naïve and memory and CD8⁺ T-cells, B-cells and plasma cells).



Discussion

- Nestin⁺ niches increase in AA, especially in sAA
  - contrasting to other inflammatory or onco-inflammatory conditions (GvHD, MPN), but similar to AML
- CXCL12⁺ niches increase in patients transforming to myeloid malignancies (n=2) but not in AA *per se*
- Upregulation of *SLAMF1, CXCL12, ANGPTL8, CTNNB1, COL1A1* and *PECAM1* in AA as a signatures of MAPK & microenvironment
- Increased adaptive immune system activity in AA

Our results 1) indicate intact and even increased (nestin)/active (CXCL12) BM niches in AA, 2) underline the understanding of AA as an autoimmune disease directly attacking HSC and not the microenvironment, and 3) suggest, considering data in AML, that the numeric increase of niche cells could be an additional explanation of the known proneness of AA to transform to AML, as both nestin⁺ & CXCL12⁺ BM stromal cells are known to pave the way in leukemogenesis.