(PF657) LARGE-SCALE MULTI-PHENOTYPE WHOLE SLIDE IMAGING ANALYSIS UNCOVERS SPATIAL NICHE ARCHETYPES ALONG THE MDS/AML CONTINUUM

Topic: 09. Myelodysplastic syndromes - Biology & translational research

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Background

Myelodysplastic neoplasms (MDS) with low (LR-MDS; <5%) or increased blasts (MDS-IB; >5%) and AML are distinct states along a continuum of abnormal hematopoiesis. While LR-MDS can be driven by immune hyperactivation, MDS-IB/AML associate with immune escape. Yet, as immunotherapies have limited activity, there is a need to better understand the spatial organization of bone marrow (BM) immune cells. Automated imaging analysis of archival BM immunohistochemistry (IHC) data can define the evolving immune microenvironment cost-efficiently and at scale.

Aims

We leveraged large-scale whole-slide imaging (WSI) analysis on multi-marker IHC data to define progenitor and immune niche archetypes in AML/MDS.

Methods

We registered serial WSIs (*QuPath*, *VALIS*) into a shared coordinate space, followed by cell segmentation, phenotyping, and density estimation. We quantified niche density, size (effective radius), composition and interaction features, and derived within-niche spatial roles from niche-restricted graphs.

Results

We integrated up to 10 stains (H&E, progenitor: CD34/CD117; myeloid: MPO/CD68/CD163/CD61; immune: CD3/CD20/CD138) from 5 normal controls (NC), 13 LR-MDS, 16 MDS-IB, and 13 AML cases across 443 BM slides, yielding a mean 147,482 single cells per slide (range 13,234–391,850). Macrophage, B and T cell density remained similar across LR-MDS, MDS-IB, and AML. However, their number relative to progenitor cells decreased from 4.39 (T cell), 1.04 (B cell) and 5.6 (macrophage) in LR-MDS to 0.58, 0.18 and 0.95 in AML ($p < 0.01$), consistent with progressive displacement of immune niches by expanding progenitor compartments.

To track organizational BM remodeling, we defined spatial niches as groups of ≥100 cells. Within niches, we classified cells as members of a core (≥10 connected cells), or adjacent, proximal and distant to it. Niche density increased from NC (mean 0.65 niches/mm²) to LR-MDS (1.13), MDS-IB (1.46) and AML (1.07). Based on the ratio of $CD3^+$ and $CD20^+$vs. $CD34^+$ and $CD117^+$ cells (cut-off 0.6), we defined immune and progenitor spatial niches. Immune niche fractions decreased from 80.7% and 78.6% in NC and LR-MDS to 46.2% and 20.9% in MDS-IB and AML ($p < 0.01$). While immune niche size remained largely stable across AML/MDS, progenitor niches showed expansion of mean core areas from NC to AML (0.350 vs. 6.42 mm²; $p<0.01$) and increased heterogeneity (mean standard deviation 0.153 vs. 7.61 mm²; $p<0.01$).

Finally, we asked how niche architectures evolved. Pseudotime analysis showed a continuous niche-remodeling across MDS/AML, and composition analysis revealed the most homogeneous immune cell infiltrate in LR-MDS. In immune niches, cell density/mm ^{2} increased for T cells from 188 in NC to 339 in LR-MDS ($p = 0.008$), 324 in MDS-IB ($p = 0.013$), and 310 in AML, while it decreased for B cells from 203 in NC to 65 in LR-MDS, 87 in MDS-IB ($p = 0.003$), and 29 in AML. Macrophage density in progenitor-niche cores decreased from 374 cells/mm² in NC to 204 in AML. By integrating niche architectures, we could classify MDS/AML cases into three niche archetypes: immune-dominated, progenitor-dominated and mixed. These categories associated with blast counts in progenitor- vs. immune-dominated MDS/AML (median 40% vs. 8%, $p = 0.043$).

Summary/Conclusion

Using automated image analysis, we reveal progressive niche remodeling across MDS/AML. This defines spatially interpretable disease archetypes that may inform risk biology and motivate survival outcome and spatial transcriptomic analyses.