ELSEVIER

Blood 142 (2023) 3220–3221

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

636.MYELODYSPLASTIC SYNDROMES-BASIC AND TRANSLATIONAL

Somatic and Germline HLA Determinants of Immune Surveillance and Escape in Myelodysplastic Syndromes

Carmelo Gurnari, MD[1,2], *Arda Durmaz*[1], *Benjamin Kroger, BS*[3], *Hussein Awada*[1], *Jacky Chen*[4], *Colin Hercus*[5], *Sébastien Hergalant, PhD*[6], *Carlos Bravo-Perez, MD*[1], *Maria Teresa Voso, MD*[7], *Jacob Scott*[8,1], *Valeria Visconte, PhD*[1], *Stephen S. Chung, MD*[3], *Jaroslaw P. Maciejewski, MD, PhD, FACP*[1], *Simona Pagliuca, MDPhD*[9,10]

[1]Department of Translational Hematology and Oncology Research, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH
[2]Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy
[3]UT Southwestern Medical Cener, Dallas, TX
[4]Cleveland Clinic Lerner College of Medicine, Cleveland, OH
[5]Novocraft Technologies Sdn Bhd, Kuala Lumpur, Malaysia
[6]Inserm UMRS1256 Nutrition-Génétique et Exposition aux Risques Environnementaux (N-GERE), Université de Lorraine, Vandoeuvre-lès-Nancy, France
[7]Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy
[8]Systems Biology and Bioinformatics Department, School of Medicine, Case Western Reserve University, Cleveland, OH
[9]Department of Hematology, Centre Hospitalier Régional Universitaire (CHRU), Nancy, France
[10]Department of Translational Hematology and Oncology Research, Taussig Cancer Institute, Cleveland, OH

While the contribution of canonical myeloid genetic drivers to myelodysplastic syndromes/neoplasms (MDS) pathobiology is well established, other genetic events operative under special circumstances, and by itself not constituting intrinsic drivers, may affect the disease course. These include genetic defects conveying resistance to specific therapies, clonally restricted DNA repair alterations favoring the accumulation of additional mutations, and/or lesions facilitating the resistance to inflammation or immune escape. Here, we focus on this latter aspect as it may shed light on the pressure exerted by immune tumor surveillance or acquired resistance to cancer immune therapies, a field that has lagged in myeloid neoplasia as compared to the dramatic changes obtained in solid tumors. We hypothesize that during MDS ontogeny and leukemia evolution a spectrum of immunological mechanisms may shape the oncogenic landscape and facilitate the emergence of clones with diverse immunogenic potential as targets, leading to selective immunotherapeutic liabilities.

We accrued a clinically and molecularly well annotated cohort of 101 MDS patients at various stages of the disease spectrum [N=51 low risk (LR)-MDS, N=32 high risk (HR)-MDS, N=18 secondary AML-sAML)]. This cohort included specific clinical subentities wherein the contribution of immune forces appears to be a prominent feature i.e., hypocellular MDS (hMDS, N=9) or MDS with co-occurring T large granular lymphocytosis (LGL) (N=5). By combining human leukocyte antigen (HLA) and T cell receptor (TCR) immunosequencing at disease onset, we leveraged our bioinformatics expertise to impute HLA mutations and losses, HLA evolutionary divergence (HED), and characteristics of T cell repertoires.

The median age of the whole cohort was 71.2 years (IQR: 63.4-77.7), and median bone marrow (BM) blast count was 3% (1-11%). Cytogenetics revealed normal karyotype in 41 patients (40%), while complex karyotype was observed in 21 (20%) and partial or complete loss of chromosome 7 in 10 cases (10%).

Comparisons with a cohort of 784 ethnicity-matched healthy individuals (HC), showed no differences in terms of locus-specific HED configurations. However, when HED scores were analyzed across the disease spectrum, we observed a heterogeneous distribution in MDS patients for the HLA-C locus, with higher values in hypoplastic and LGL-associated MDS as compared to HR diseases ($p = 0.0068$) and sAML ($p = 0.0409$).

The screening for immune evasion highlighted the presence of both somatic mutations and losses in the HLA region in 14 patients, with both type of alterations found in 1 case. Of those, 6 patients (20% LGL-MDS, 5% LR-MDS and 17% sAML) harbored HLA mutations (in HLA-A, B, C and DPB1 loci), whereas HLA losses were observed in 9 patients (22% hMDS, 5% LR-MDS, 10% HR MDS, 11% sAML) almost exclusively in class II alleles (chiefly DPB1, DRB1 and DPA1).

When exploring the degree of immunocompetence by TCR immunosequencing as a proxy, we found a higher degree of diversity (imputed via inverse Simpson index) as compared to healthy controls (p=1.5e-07), possibly in relationship to diverse

T cell responses across the disease spectrum. However, no difference between MDS sub-entities was found. Of interest is that the maximal productive frequency (an indicator of the degree of T cell expansion) was higher in patients with hMDS and LGL-associated MDS as compared to HR-MDS (p=0.0079). Finally, inter-sample comparisons of shared clonotypes showed a high degree of overlap with regards to TCR repertoires among MDS as compared to healthy subjects.
Our data emphasize the adaptive immune-molecular network underpinning MDS development. HLA constellations and their interactions with TCR repertoires may create selective immune pressure. Somatic HLA aberrations may serve as a marker of ongoing immune pressure and correspond to oligoclonal T-cell expansions and variations in TCR diversity. While virtually no HLA mutations have been previously found in AML/MDS, we show a relatively higher frequency of HLA aberrations in hMDS and MDS-LGL, immunologically stressed scenarios reminiscent of aplastic anemia and post-allogenic transplant AML/MDS cases, whereby respectively 36% [1] and 38% [2] of patients harbored HLA lesions as a mean of escape from cytotoxic lymphocytes or allogeneic Graft-vs-Leukemia reactions.

Disclosures Voso: *Astra Zeneca:* Speakers Bureau; *Jazz:* Other: Advisory Board; *Celgene/BMS:* Other: Advisory Board; *Syros:* Other: Advisory Board; *Novartis:* Speakers Bureau; *Abbvie:* Speakers Bureau; *Jazz:* Speakers Bureau; *Astellas:* Speakers Bureau; *Novartis:* Research Funding; *Celgene/BMS:* Research Funding, Speakers Bureau. **Maciejewski:** *Novartis:* Honoraria, Speakers Bureau; *Alexion:* Membership on an entity's Board of Directors or advisory committees; *Regeneron:* Consultancy, Honoraria; *Omeros:* Consultancy.

https://doi.org/10.1182/blood-2023-178890