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POSTER ABSTRACTS

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Stable MGUS and SMM Are Characterized By Distinct Senescent Features in the Pre-Malignant Plasma Cells and the Proximate Bone Microenvironment

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Multiple Myeloma (MM) progresses from monoclonal gammopathy of undetermined significance (MGUS) and/or smoldering MM (SMM). Despite similar primary genetic events as MM, MGUS and SMM PCs are non- or low-proliferative. Since oncogene activation and DNA damage drive senescence growth arrest to promote immune clearance of potentially malignant cells, we hypothesized that MGUS and SMM pre-malignant PCs exhibit senescence features.

To test this, we performed gene set enrichment analysis (GSEA) of a published human PC gene array dataset (GSE5900) comparing normal, MGUS, and SMM PCs for custom senescence phenotyping gene sets (Senescence Up, SenUp; Senescent Cell Anti-Apoptosis Pathways, SCAPs; Senescence Growth Arrest, SenGA; Inflammatory Senescence Associated Secretory Phenotype, iSASP; Interferon SASP, IFN-SASP) versus biological aging gene sets (SenMayo; CellAge). MGUS and SMM PCs exhibited significant enrichment (NES>1.5, q<0.05) for senescence gene sets SenUp, SenGA, and SCAPs compared to normal PCs, with no enrichment for aging gene sets. MGUS PCs were also enriched for iSASP (NES=1.4, q=0.11), whereas SMM PCs were enriched for IFN-SASP (NES=2.3, q<0.05), characteristic of late-senescence. Thus, both MGUS and SMM PCs show enrichment of senescence gene sets compared to normal PCs with differential SASP profiles.

Next, we evaluated MGUS, SMM, and MM patient PCs isolated by magnetic sorting for histological senescence features. PCs were immunostained for LMNB1 and HMGB1, and fluorescent *in situ* hybridized for α -satellite. Cellular senescence was defined as loss of \geq 50% nuclear membrane LMNB1, loss of HMGB1, and \geq 2 senescence-associated distensions of satellite (SADS) per nuclei. PCs from MGUS patients (N=12) exhibited increased percentage of senescent PCs (26.9±4.1%, Mean±SEM, p<0.0001) compared to SMM (11.0±1.9%, N=19, p<0.0001) and MM (11.6±1.5%, N=11, p<0.001). A subset analysis of SMM patients for which disease stability was known (\geq 2 years, N=6-8) showed no differences. These results demonstrate that the percentage of senescent PCs is increased in MGUS but not SMM PCs compared to proliferative disease.

To assess PC senescence in the native bone marrow microenvironment (BMME), we evaluated trephine bone biopsies from MGUS and SMM patients that progressed or not to MM \leq 10 years, as well as newly diagnosed MM. Biopsies were immunos-tained for CD138, LMNB1, and HMGB1. Whole biopsy images were analyzed using the artificial intelligence-based software HALO. Cells were classified as senescent if they were double negative and non-senescent if they were double positive for LMNB1 and HMGB1. The percentage of non-senescent PCs increased with progression to MM and positively correlated with total PC burden (R=0.52, p<0.0001), reflective of proliferative disease. Senescent PCs correlated with total senescent BMME (R=0.87, p<0.0001), consistent with a role for senescent cells to drive paracrine senescence. We performed proximity analysis to evaluate the cellular composition within 25um of senescent and non-senescent PCs. As expected, non-senescent PCs exhibited a significantly greater percentage of proximate non-senescent BMME in all groups (p<0.0001). In contrast, senescent

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PCs in stable MGUS (N=16) and SMM (N=14) were equally surrounded by senescent and non-senescent BMME. In progressing MGUS (N=21) and SMM (N=20), as well as MM (N=18), senescent PCs exhibited significantly reduced senescent BMME in their proximate environment (p<0.05). This suggests that senescent PCs in progressive disease, in contrast to stable disease, fail to drive local paracrine senescence responses.

These data demonstrate that PCs from stable MGUS and SMM patients exhibit senescence features, with isolated PCs from stable MGUS showing increased senescence gene expression and histologic features. While stable SMM also exhibits senescence gene expression, they lose morphological features of senescence and show a preferential IFN SASP. Within the bone compartment, senescent PCs in stable MGUS and SMM exhibit the expected proximity to senescent BMME. In contrast, progressing MGUS and SMM, as well as NDMM, show a loss of proximate senescent BMME. Given the role of senescence to drive inflammation to clear potentially tumorigenic cells, these data support that failure to drive paracrine senescence may be key to the immune escape of pre-malignant cells in MGUS and SMM.

Disclosures No relevant conflicts of interest to declare.

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