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POSTER ABSTRACTS

631.MYELOPROLIFERATIVE SYNDROMES AND CHRONIC MYELOID LEUKEMIA: BASIC AND TRANSLATIONAL

Lactate Transporters Modulate Stromal Cell Remodeling in Myeloproliferative Neoplasms (MPN)

Daniele Tibullo[1], Mariarita Spampinato[2], Andrea Duminuco[2,3], Enrico La Spina[4], Sebastiano Giallongo[5], Alessandra Romano, MDPhD[6], Grazia Scandura[4], Tatiana Zuppelli[5], Rosario Caltabiano[5], Lucia Salvatorelli[5], Giovanni Li Volti[5], Francesco Di Raimondo, MD[7], Cesarina Giallongo, PhD[8], Giuseppe Alberto Palumbo, MD[9]

[1]Università degli Studi di Catania, Catania, ITA
[2]university of catania, catania, Italy
[3]Department of Clinical Haematology, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom
[4]Divisione di Ematologia, Dipartimento di Chirurgia e Specialità Medico Chirurgiche, Università degli Studi di Catania, Catania, Italy
[5]University of catania, catania, Italy
[6]Divisione di Ematologia, Dipartimento di Chirurgia e Specialità Medico Chirurgiche, Università degli Studi di Catania, Tremestieri Etneo, Italy
[7]Haematology, A.O.U. Policlinico "G. Rodolico-San Marco", Catania, Italy
[8]Università degli Studi di Catania, Catania, ITA
[9]Department of Scienze Mediche, Chirurgiche e Tecnologie Avanzate "G.F. Ingrassia", University of Catania, Catania, Catania, Italy

Introduction. Philadelphia-negative myeloproliferative neoplasms (MPNs) include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). The diagnostic approach proposed by the World Health Organization (WHO) uses clinical features, bone marrow (BM) morphology, karyotype and molecular genetic tests to classify MPN subtypes. The BM morphology includes cellularity, erythropoiesis, and neutrophil granulopoiesis in context with specific features of megakaryocytes as well as the BM fiber content, especially in early-stage myelofibrosis that present with thrombocytosis and clinically mimic ET. Since alteration of hematopoiesis is constantly associated with profound modifications of the bone marrow (BM), we hypothesize that CD34+ cells from PMF can actively produce lactate and thus rewiring metabolism of immune cells and mesenchymal stromal cells (MSCs). In turn, this could favor immune evasion and remodeling of BM niche. ***Methods.***Cell proliferation was assessed in vitro on primary MSCs, HS-5 cell line, and PBMC cells. Protein expression was performed by Western blot and immunofluorescence assay. The NCBI GEO database was used to select transcriptome datasets and to analyze gene expression in PMF patients. Cytokine detections were performed by Multiplex immunobead assay technology. An adult TPO-mimetic-induced PMF Zebrafish model was used for in vivo evaluation. An immunohistology assay was performed in MPN BM biopsies. ***Results.***CD34+ cells from PMF patients significantly upregulated the lactate monocarboxylate transporters (MCT-1 and -4) compared to healthy CD34+ cells. Consistently, lactate concentration was higher in PMF sera compared to healthy controls. Since PMF patients showed an increased percentage of circulating immunosuppressive cells such as G- and M-MDSC and Treg, we incubated healthy peripheral blood mononucleated cells (PBMNCs) with PMF sera in the presence or absence of MCT1inhibitor (AZD3965) to evaluate the role of lactate in the expansion of these immunological subsets. We found an expansion of both Treg and M-MDSCs, which was reverted after blocking of circulating lactate by AZD3965. In order to study the effect of lactate in BM remodeling, we treated in vitro healthy MSCs with lactate (20 mM) for 24h. Interestingly, lactate induced a modification of extracellular matrix organization, as demonstrated by increased reticulin and collagen deposition and metalloproteases (MMP9, MMP2). Moreover, lactate increased calcium deposit and soluble osteogenic molecular signals (i.e. osteoprotegerin, osteonectin). These results also were obtained after incubation with PMF sera and were reverted after AZD3965 treatment. Since it has been demonstrated the role of cancer-associated fibroblast (CAF) in cancer development through ECM remodeling, we next evaluated the expression of CAF markers in MSCs after lactate exposure. α-SMA, FAP1, and TGFβ were found upregulated and this effect was reverted by AZD3965. Finally, we further confirmed these results in a Zebrafish animal model of PMF. Interestingly, in Zebrafish model we observed a reduction of MCT4 expression that was confirmed in the PBMNCs of the PMF patients. **Conclusions**. Inhibition of lactate metabolism may represent a strategy to inhibit

cancer cells and contribute to restoring the anti-cancer immune response. Therefore, lactate metabolism may represent a promising target to counteract inflammation, osteosclerosis, and fibrosis in PMF patients.

Disclosures Palumbo: *Novartis:* Consultancy, Honoraria, Speakers Bureau; *GSK:* Consultancy, Honoraria; *BMS:* Consultancy, Honoraria, Speakers Bureau; *ASTRA ZENECA:* Consultancy, Honoraria; *ABBVIE:* Consultancy, Honoraria, Speakers Bureau; *MorphoSys:* Consultancy, Honoraria.

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