GLYCOSYLATION-DEPENDENT CIRCUITS SYNCHRONIZE THE PRO-ANGIOGENIC AND IMMUNOREGULATORY FUNCTIONS OF MYELOID-DERIVED SUPPRESSOR CELLS IN CANCER

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Myeloid-derived suppressor cells (MDSCs) favor tumor progression and therapy resistance by reprogramming antitumor immunity and promoting angiogenesis. To elucidate the mechanisms that synchronize these functions, we investigated the role of glycosylation-dependent, galectin-1 (Gal1)-driven circuits in coupling immunoregulatory and pro-angiogenic activities of MDSCs. Flow cytometry and HPLC-HILIC/WAX revealed an activation-dependent glycan profile in monocytic and polymorphonuclear MDSCs (p=0.03) that controlled Gal1 binding and was more prominent in tumor microenvironments. Exposure to Gal1 led to concomitant activation of immunosuppression and angiogenesis programs in bone marrow derived MDSCs. Flow cytometry of Gal1-conditioned MDSCs showed higher expression of immune checkpoint molecules, including programmed death ligand-1 (PD-L1) (p=0.005) and indoleamine 2,3-dioxygenase (IDO) (p=0.037) and greater production of reactive oxygen species (ROS) and nitric oxide (NO) (p=0.02). *In vitro,* Gal1-conditioned MDSCs showed greater T-cell suppressive capacity (p=0.03) and higher IL-10 (p=0.04) and IL-27 (p=0.003) secretion. These effects were accompanied by enhanced endothelial cell migration, tube formation, 3D-sprouting and vascularization (p<0.05). *In vivo*, Gal1-conditioned MDSCs accelerated tumor growth (p=0.001) and fostered immune evasion and vascularization programs in Gal1-deficient colorectal tumors. Mechanistically, mass spectrometry, immunoblot and blocking assays identified the CD18/CD11b/CD177 complex as a bona fide Gal1 receptor and STAT3 as a key signaling pathway coupling these functions. Accordingly, a combined algorithm that integrates Gal1 expression and MDSC phenotype, showed critical prognostic value by delineating the immune landscape and clinical outcome of human cancers. Thus, glycosylation-dependent Gal1-driven circuits favor tumor progression by coupling immunoregulatory and pro-angiogenic programs of MDSCs via CD18- and STAT3-dependent pathways.

TRANSCRIPTOMIC STUDY REVEALS GENES AND BIOCHEMICAL PATHWAYS ASSOCIATED WITH CLINICAL EVOLUTION OF PATIENTS WITH CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Acute lymphoblastic leukemia (ALL) is the most incident pediatric cancer. While considerable progress has been made on treatment efficacy and survival rates, about 15-30% of patients relapse and/or die. We aimed to identify gene-expression profiles in childhood ALL that could help better predict disease outcome, response to treatment and therapy-related toxicity. We collected 39 bone marrow samples at time of diagnosis of ALL from 3 hospitals from Argentina. Total RNA was isolated to perform transcriptome analysis (RNAseq). Clinico-pathological characteristics and disease outcome were evaluated and recorded by oncohematologists. We analyzed differential gene expression (DGE) and gene set variation analysis (GSVA) comparing: early response to prednisone, event-free survival, risks group, acute toxicity and minimal residual disease at day 15. We observed that about 30% of dysregulated genes were non-coding RNAs, being long non-coding RNA (lncRNA) the predominant biotype. We identified 6 differentially expressed pathways relevant to ALL biology (p<0.01) and 7 lncRNAs (MIR99AHG, LINC02866, ZNF385D-AS2, LINC02848, MYO18B-AS1, Lnc-PPDPFL-1, Lnc-RIT2-2; padj≤0.05) among ALL risk groups. Because the biological activity of most lncRNAs is still unknown and under the hypothesis that lncRNAs modulate biochemical pathways, we calculated the correlation between significant lncRNA and pathway expressions. We found that MYO18B-AS1 positively correlated with “inactivation of MAPKK activity” (r=0.4;p=0.02) and LINC02866 negatively correlated with “CXCR3 chemokine receptor binding” (r=-0.4;p=0.02) and “transmembrane receptor protein tyrosine phosphatase activity” (r=-0.4;p=0.01). This study identified dysregulated lncRNAs and biochemical pathways that might be relevant in the pathology of childhood ALL. The analysis of these gene-expression profiles at diagnosis might help improving risk stratification, therapy efficacy and reducing the occurrence of relapse and toxicity.