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Immunometabolic actions of trabectedin and lurbinectedin on human macrophages: relevance for their anti-tumor activity

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In recent years, the central role of cell bioenergetics in regulating immune cell function and fate has been recognized, giving rise to the interest in immunometabolism, an area of research focused on the interaction between metabolic regulation and immune function. Thus, early metabolic changes associated with the polarization of macrophages into pro-inflammatory or pro-resolving cells under different stimuli have been characterized. Tumor-associated macrophages are among the most abundant cells in the tumor microenvironment; however, it exists an unmet need to study the effect of chemotherapeutics on macrophage immunometabolism. Here, we use a systems biology approach that integrates transcriptomics and metabolomics to unveil the immunometabolic effects of trabectedin (TRB) and lurbinectedin (LUR), two DNA-binding agents with proven antitumor activity. Our results show that TRB and LUR activate human macrophages toward a pro-inflammatory phenotype by inducing a specific metabolic rewiring program that includes ROS production, changes in the mitochondrial inner membrane potential, increased pentose phosphate pathway, lactate release, tricarboxylic acids (TCA) cycle, serine and methylglyoxal pathways in human macrophages. Glutamine, aspartate, histidine, and proline intracellular levels are also decreased, whereas oxygen consumption is reduced. The observed immunometabolic changes explain additional antitumor activities of these compounds and open new avenues to design therapeutic interventions that specifically target the immunometabolic landscape in the treatment of cancer.