Pattern of IRG1/Acod1 Expression in the Tumor Microenvironment as Revealed by Single-Cell RNA Seq Analysis

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Acod1 is a gene that codes for immune response gene 1 (IRG1), an enzyme that converts TCA cycle intermediate cis-aconitate into itaconate. Itaconate exerts multiple biological effects, from suppression of bacterial pathogen growth to immunosuppressive activity towards immune cells. High Acod1-expressing cells produce more enzymes, leading to higher itaconate production. It has been shown that Acod1 is expressed in myeloid cells isolated from cancer patients and may play a role in tumor progression and patient outcomes. However, Acod1 expression within the tumor and the specific cell types responsible for expressing Acod1 within the tumor immune microenvironment are largely unknown. Therefore, I investigated Acod1 expression in 7 murine tumors from several different cancers using publicly available scRNA-seq data, an innovative and comprehensive approach. The study found that the highest levels of Acod1 expression were associated with two separate populations expressing markers consistent with myeloid-derived suppressor cells (MDSCs). Between these populations, the clusters expressing granulocytic markers, likely polymorphonuclear MDSCs (PMN-MDSCs), expressed the highest levels of Acod1 while Acod1 expression was lower in cells expressing monocytic MDSC (M-MDSC) markers. Spearman correlation analysis showed a significant concordance of expression between IRG1 and a set of 22 genes, suggesting an activated neutrophil phenotype stimulated by Interferon and/or Toll-like receptor pathways. These observations suggest that PMN-MDSCs exert immune suppression within the tumor microenvironment through itaconate production. Further characterization of these populations may lead to cancer therapeutic targets, helping reduce tumor immune suppression and enhance therapeutic outcomes.