Immunopathology of leishmaniasis: a spatial perspective on the regulation of immune checkpoint molecules.

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The aberrant expression of immune checkpoint (IC) molecules is now well established as a mechanism regulating local immunity in cancer, autoimmunity, and infectious diseases, including those caused by parasitic protozoans. Focusing on the analysis of human skin biopsies from patients with various forms of cutaneous leishmaniasis and from volunteers enrolled in a human challenge study, we have applied spatial transcriptomics combined with conventional immunohistology to explore the diversity in cellular expression of important IC molecules (e.g. PD-L1, IDO1) and the impact of intracellular parasitism on their expression. Furthermore, using techniques in spatial mapping such as Delaunay triangulation, we have characterised the neighbourhood surrounding IC-expressing myeloid cells as a means of identifying the cellular and molecular pathways leading to IC molecule expression. Recent data will be discussed that points to an important role for IL-32γ-expressing $CD8^+$ T cells as drivers of IC molecule expression during human cutaneous leishmaniasis and hence as contributors to the immune dysfunction that limits the action of immune-dependent anti-leishmanial drugs.