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Abstract

Bone marrow-derived myeloid cells are a heterogeneous group of leukocytes that play key roles in response to intestinal injury. We have previously reported myeloid cell differentiation is regulated by histamine, produced by the enzyme histidine decarboxylase (HDC), which is expressed in a large subset of immature myeloid cells that contribute to colorectal cancer. We have now discovered that HDC also marks a unique subset of myeloidbiased hematopoietic stem cells (MB-HSC) that are maintained in quiescence by histamine signaling from myeloid daughter cells. In response to injury or cancer, this HDC+ myeloid lineage is mobilized from the BM, thus reducing histamine and activating the MB-HSC to produce more progeny that contribute to epithelial regeneration and immunosuppression. Insufficient histamine signaling leads to overexuberant inflammatory responses, HSC exhaustion, and increased lethality following DSS colitis. Preliminary data from our lab indicate that HDC+ myeloid cells are a major source of Wnts and PGE2, highly express the immune checkpoint ligand PD-L1, and in the setting of carcinogenesis constitute the major myeloid suppressor population. Thus, we hypothesize that HDC+ HSC plays a unique role in intestinal regeneration and is regulated by histamine-secreting myeloid cells in the ISC niche.We propose 3 specific aims. **(1).** Does excessive loss of bone marrow histamine production contribute to HSC exhaustion and hyper-inflammatory response in acute, severe colitis? We will use DTA ablation of HDC+ myeloid cells, HDC knockout mice and DSS colitis to examine the impact on HSCs during intestinal injury. **(2).** Is the HDC+ myeloid lineage important for intestinal regeneration? We will examine the effects of DTA ablation of HDC+ myeloid cells, and conditional knockout of Porcupine and COX-2, to determine their contribution to ISCs and intestinal regeneration. (3). Is the HDC+ myeloid lineage the principal source of myeloid suppressors that contribute to early intestinal preneoplasia? We will use the AOM/DSS model in combination with bone marrow transplants, adoptive transfer, DTA ablation and CD8+ T cell depletion to determine the role of HDC+ cells in CRC and whether this depends on inhibition of CD8+ T cells.