ABSTRACT

The enzyme histidine decarboxylase (HDC) converts L-histidine to histamine, a biogenic amine that functions in numerous physiologic processes, but has increasingly been linked to immune regulation. Work from our laboratory using HDC-EGFP BAC transgenic reporter mice has demonstrated that HDC is highly expressed in CD11b+Ly6G+ immature myeloid cells (IMCs) that exhibit cell surface markers similar to myeloid-derived suppressor cells (MDSCs) or tumor-associated neutrophils (TAN). These HDC-expressing cells are recruited early on in an AOM/DSS model of colorectal carcinogenesis. HDC-/- mice that are deficient in histamine production exhibit markedly increased inflammatory responses to AOM/DSS and thus increased colon carcinogenesis, due largely to deficient myeloid maturation. HDC-/- mice show increased circulating CD11b+Ly6G+ IMCs and decreased mature neutrophils and macrophages, due to a requirement for histamine for normal maturation and differentiation of CD11b+Ly6G+ myeloid progenitors. Transplant of HDC deficient bone marrow to wild type recipients results in increased CD11b+Ly6G+ cell mobilization and reproduces the cancer susceptibility phenotype. CD11b+Ly6G+ IMCs from HDC-KO mice show increased proinflammatory cytokine expression and induce greater growth of colon cancer xenografts. IMCs accumulate in early stages of mouse and human colonic neoplasia, due to downregulation of HDC gene expression by cancer cells leading to inhibition of myeloid cell maturation, suggesting a novel mechanism by which tumors promote an active tumor microenvironment. Taken together, these data indicate key roles for HDC/histamine in myeloid cell differentiation, and CD11b+Ly6G+ IMCs in early colon cancer development. We are proposing four specific aims: **(1) Are HDC-expressing CD11b+Gr1+ cells myeloid precursors that give rise to mature monocytes and granulocytes and other cell types?** We will utilize HDC-BAC-Cre-ERTM mice developed in our laboratory to trace the development and differentiation of the myeloid cell lineage, both in vitro and in vivo. **(2) How are HDC-expressing IMCs recruited during carcinogenic stimuli?** We will examine the role of IL-1β, IL-6, and RAGE ligands (S100A8/A9), and test the effect of IL-1β blockade and RAGE deletion on IMC recruitment. **(3) How do tumors downregulate HDC to inhibit myeloid cell differentiation and maturation?** We will examine changes in methylation of the HDC CpG promoter sites during co-culture of IMCs with tumor cells, and explore the possible role of TGF-β in modulating myeloid cell differentiation. **(4) Are HDC-expressing IMC cells critical to the initiation and promotion of colorectal cancer?** HDC-BAC-Cre-ERTM mice will be crossed to Ikkβ F/F and DTR F/F mice, and we will also explore the importance of histamine in carcinogenesis.