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DISSERTATION

"Carbonic anhydrase 1 promotes mast cell development"

by

Everett Henry

Infection, Immunity and Inflammation Program

B.A. 2011, Drew University, NJ

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Cancer Center G1196

ABSTRACT

Type 2 cytokine-mediated inflammation is necessary for the development of protective immunity to helminth parasites but also causes the inflammation associated with allergies and asthma. Type 2 cytokine responses promote a complex but coordinated interplay of immune cells including hematopoietic stem/progenitor cells (HSPCs) that can differentiate into other type 2-promoting effector cells including mast cells. Further, recent studies have demonstrated that the development of HSPCs into mast cells represents a critical component of the type 2 inflammation. Our transcriptional analysis revealed that elevated carbonic anhydrase (Car) enzyme expression in type 2-associated HSPCs is concomitant with their increased mast cell potential. Here, we show that pharmacologic inhibition of Car enzymes impairs mast cell-dependent immunity to the helminth parasite *Trichinella spiralis* and the induction of mast cell responses in the context of food allergy-like disease. Additionally, HSPCs genetically edited to delete Carbonic anhydrase 1 exhibited a reduced capacity to develop into mast cells. Collectively, these data suggest that Car1 operates as a positive regulator of mast cell development. To further investigate the role that Car1 plays in mast cell lineage commitment, we generated a Car1-ehnacned green fluorescent protein (eGFP) reporter mouse model and investigated Car1 expression in stem cell populations. Remarkably, Car1 expression was found to be limited to a small population of progenitor cells in the bone marrow and spleen. Sort-purification of Car1-expressing cells revealed they possessed dual potential to develop into mast cells and erythrocytes. These data support a growing body of literature suggesting that mast cells and erythrocytes share common developmental origins and further highlight the potential of Car1 as a therapeutic target capable of regulating mast cell-mediated inflammation.