

Eosinophils role in cancer

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Dodagatta-Marri E. Eosinophils role in cancer. J Blood Disord Treat. 2018;1(2):30-31.

Key Words: *Eosinophils; Eosinophil homeostasis.*

Eosinophils belong to the subpopulation of granulocytes, which are characterized by their bilobed nuclei, large granules and the property of acidophilic staining. In 1870's by Paul Ehrlich identified them in the peripheral blood and nomenclature is due to their property of acidic staining of their granules [1]. Eosinophils are present in all vertebrates, evolved before adaptive immune system, they mature in bone marrow and upon activation, migrate to organs and tissues expressing receptors for activation, migration, adhesion and recognition (Toll-like Receptors-TLRs and Pattern Recognition Receptors-PRRs). Eosinophils derived from CD34+CD117+ pluripotent hematopoietic stem cells upon maturation in bone marrow, eventually enter into the blood circulation in humans [2]. Sialic acid-binding Ig-like lectins 8 (Siglec)-8 in human [3] and Siglec F [4] are the markers expressed on mature eosinophils, express IL-5 receptor alpha subunit and C-C Chemokine Receptor (CCR), also known as eotaxin receptor or CD125, which are regulated by three main chemokines-eotaxin-1 (CCL11), eotaxin-2 (CCL24) and eotaxin-3 (CCL26). Interleukin (IL)-13 induces eotaxins in gastrointestinal (GI) tract through Innate helper Lymphoid Cells (ILC). IL-5, IL-3 and Granulocyte Macrophage Colony-stimulating Factor (GM-CSF) are crucial regulating factors in the development of eosinophils [5, 6]. IL-5 is important in growth, differentiation and activating factor in human eosinophils, β subunit of IL-5 receptor shares with the receptors for IL-3 and Granulocyte-macrophage Colony-stimulating Factor (GM-CSF). They help eosinophils in maturation and development with the help of GATA-1, a transcription factor in the bone marrow mediating eosinophil survival through K κ B induced Bcl-xL, which inhibits apoptosis [7]. IL-33 at various stages of maturation, activation, development of eosinophils and their progenitors within tissue in the bone marrow and for basal eosinophil homeostasis, can directly activate eosinophils inducing upregulation of the adhesion molecule CD11b and the activation marker CD69 [8-10]. Levels of eosinophils in blood and peripheral tissues decrease in the IL-5 deficiency in mice. It is produced by type-2 Innate Lymphoid Cells (ILC2), Th2 cells, mast cells, invariant NKT cells and eosinophils. Their intracellular content granules containing crystalloid core compound Major Basic Protein (MBP), ribonucleases Eosinophil Cationic Protein (ECP), Eosinophil-derived Neurotoxin (EDN) and eosinophil peroxidase distinctively recognize them [11]. MBP-1 and MBP-2 cytotoxicity increases the membrane permeability through surface charge interactions [11]. ECP has ribonuclease activity, helminthes toxicity and cytotoxicity; it induces pores into the membranes of the cells on pathogens by facilitating the cytotoxic particles into the pathogen, they mediate Antibody-dependent Cellular toxicity (ADCC) against helminthes. ECP and EDN degrade single-stranded RNA viruses by ribonuclease activity and in case of bacterial infections; CC3 ligands deprive the mitochondrial traps containing ECP and MBP. EDN acts like a ligand to TLR2 activating the dendritic cells through TLR2/MyD88 signaling pathway. They also have mediators like leukotrienes, prostaglandins and platelet-activating factor helping in chemotaxis and activation [12].

Eosinophils release cytokines after degranulation to produce T helper type 2 (Th2) chemo-attractants in allergic diseases, Prostaglandin D2 (PGD2R), a chemo-attractant receptor-homologous molecule expressed by Th2 cells, known to regulate them. EDN promotes the antigen-specific Th2 response and migration-maturation of dendritic cells. Indoleamine 2,3-dioxygenase (IDO) helps in the polarization by the apoptosis of Th1 cells and also change the fate of the Treg cells. Eosinophils known to express MHC class II and co-

stimulatory molecules CD40, CTLA-4, CD80/86, which regulate the T-cell activation, proliferation and cytokine secretion and have an effect on various innate and adaptive immune cells and presenting antigens to be processed. They secrete cytokines that enhance T-cell proliferation and activation [13]. Mast cell functions regulated by eosinophils releasing cytokines, granular molecules, MBP, EPO and ECP thus secreting histamines, TNF-, IL-8, PGD-2 and GM-CSF. Mast cells have a major role in eosinophil for the production and vice versa. Transforming growth factor- β has significant role on the immune cells from regulating to deciding the fate of the cells like macrophages, Th1, Th2 and B cells and these granulocytes release TGF- β [14]. Based on tissue resident eosinophils, the functions vary depending on the cytokine release. Under normal conditions, eosinophils in GI tract, mammary glands, lung, adipose tissue, uterus, spleen and lymph nodes maintains homeostasis for normal development/morphogenesis through the secretion of cytokines and growth factors like TGF- β [15].

EOSINOPHILS AT TUMOR SITE

Eosinophils migrate to the inflamed tissues and tumor microenvironment through adhesion to the integrins on the endothelial cells after activation. CCR3 gets activated by the eotaxins and RANTES (Regulated on Activation, Normal T cell Expressed and Secreted), which mediate the attraction of the eosinophils to the inflamed tissues. Cytokines, chemokines and adhesion molecules play major role in the eosinophil migration to the tumor site. Damage-Associated Molecular Patterns (DAMPs) hire eosinophils through the High Mobility Group Box 1 protein (HMGB1), IL-1 α and IL-33. Damaged or necrotic cells activates HMGB1 triggering the activation of immune cells and intervenes cell proliferation, differentiation, inflammation and cell migration [16,17]. It acts as chemo-attractant for eosinophils by activating TLR2 and TLR4. IL-33 is also released under stress, damaged cells or necrosis which, forms a complex with IL-1R4, found in many cancers recruiting eosinophils to the site and activating IL-5. Eosinophils are recruited by Vascular Endothelial Growth Factors (VEGFs) by mast cells and macrophages [18,19].

ROLE OF EOSINOPHILS IN CANCER

Eosinophils anti-tumorigenic activity could be seen by the cytokines, chemokines, growth factors etc. that are secreted and recruited. They also express natural killer cell-associated killing receptors such as 2B4 (CD244) targeting the malignant B cells. Depletion of regulatory T cells (Tregs) in a melanoma model, eosinophils promoted the recruitment of CD8+T cells, polarized proinflammatory macrophages taking the mode towards anti-tumorigenic [20].

Eosinophils also store and release growth factors and cytokines that stimulate proliferation of fibroblasts and promote angiogenesis like TGF β , CCL18, FGFs (Fibroblast Growth Factors), IL-6, VEGF (Vascular Endothelial Growth Factor) [21,22].

CONCLUSION

Eosinophil derived cytokines, chemokines, growth factors that help in the activation of T cell mediated tumor killing and antigen presentation of immune cells. Eosinophil participate in various physiological and pathological processes, migration of eosinophils to the Tumor Micro-

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Received: November 30, 2018, Accepted: December 04, 2018, Published: December 14, 2018



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environment (TME) and releasing various cytokines, chemokines and growth factors suggests that it plays a pivotal role. However, more detailed research needs to be carried out in order to understand the complete mechanisms. There seems to be orchestra of things that happen in the TME, which include all the immune cells and tumor cells and their interactions lead to various outputs. Detailed understanding of these “once not so important” cells could be used as biomarkers in cancer immunotherapy for clinical purposes.

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