Eosinophils and Melanoma: A Review

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INTRODUCTION

- Melanoma is one of the fastest-growing malignancies worldwide and the most lethal cutaneous cancer.
- In the past decade, introduction of immune checkpoint blockers (ICBs) prompted a paradigm shift in the treatment of metastatic melanoma, fundamentally improving survival rates in metastatic disease from 10% to over 50% at 5-years.
- Eosinophils have been implicated as an important intermediary of the TME in melanoma, of which, studies have shown to predict responses to ICBs.
- Additionally, serum eosinophil levels have been associated with improved survival outcomes, suggesting potential utility of eosinophils as a prognostic marker for patients with melanoma.

FUNDAMENTAL EFFECTOR MECHANISMS

- Eosinophils modulate the TME, augmenting the recruitment of additional eosinophils, potentiating tumor-associated eosinophils.
- Metalloproteases (MMPs) aid in the leukocytic invasion of the TME along with eosinophilic tumor infiltration.
- Increased eosinophilic cationic protein (ECP) conferred reduction in tumor burden and tumor cell viability in experimental studies.
- The secretion of cytokines from eosinophils can influence the balance of T1 and T2 CD4+ T cell populations via interactions with CTLA-4 surface antigens.
- Tumor clearance of melanoma lung metastases by Th2 cells was dependent on eosinophil-mediated Th2 polarization of CD4+ T cells.
- Eosinophils secrete IL-1α, self-inducing HLA-DR expression and establishing its role in the function of eosinophils as APCs.

CLINICAL IMPLICATIONS OF EOSINOPHILS

- For the most part, preclinical studies are favorable towards the anti-tumor effects of eosinophilic tumor infiltration.
- Given the interaction between eosinophils/eosinophil-related proteins and the adaptive immune system targeted by immunotherapy, eosinophilic profiles may serve as biomarkers to predict which patients will respond to immunotherapy treatment for melanoma.
- Specifically, in the setting of melanoma treatment, peripheral blood eosinophil counts are associated with favorable clinical outcomes in patients treated with ipilimumab and pembrolizumab.
- Studies investigating eosinophils have reported that higher pre-treatment eosinophil counts and increasing eosinophil counts with treatment were positively correlated with prolonged overall survival, suggesting that eosinophils may be an important contributor for better predicting responses to checkpoint blockade.

CONCLUSION

- As ICB therapies become first-line treatments for cancers, including melanomas, it is paramount that responders and non-responders are identified and subsequently treated appropriately.
- Eosinophils play an important and diverse role in the immunology and predicting clinical outcomes in melanoma and other anti-tumorigenic factors listed in red.
- On the other hand, eosinophilia is an unfavorable prognostic indicator in those cancers listed in green as pro-tumorigenic; and mixed in those labeled in purple as having “both” pro and anti-tumorigenic effects.

PROGNOSTICATOR IN MELANOMA AND OTHER HUMAN CANCERS

- An overabundance of eosinophils at the tumor site or in the peripheral blood is a favorable prognostic factor in melanoma and other anti-tumorigenic factors listed in red.

Figure 1: Visual representation of eosinophils and their essential contents and functions.
- The physiologic function and recruitment of eosinophils are primarily mediated by surface molecules, cytokines and chemokines.
- There is evidence to suggest that tumor cell growth and invasion are modulated by eosinophilic degranulation of cytokines, chemokines, growth factors, enzymes, and lipid mediators.
- While eosinophils historically play a prominent role in atopic disease, there is evidence to suggest eosinophils regulate T and B-cell populations and increase granulocytic cell survival in inflammatory tissue and promote a Th1 CD4+ along with a Th2 CD4+ immune response as well.

Figure 2: Cytotoxic action of the eosinophil via interaction with other immune cells once released from the bone marrow.

Figure 3: Representation of the anti-tumorigenic and pro-tumorigenic roles of eosinophils in various human cancers.