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MEETING ABSTRACT

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Myeloperoxidase positively regulates non-small-cell lung cancer development

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Background: Myeloperoxidase (MPO) is predominantly expressed by neutrophils and expressed in their primary granules. It is a heme peroxidase that catalyses the reaction of hydrogen peroxide with halides (Cl^- and Br^-) and pseudo-halide (SCN^-) to generate powerful oxidants that can have important biological effects by modifying proteins, lipids and DNA. Neutrophils are a prevalent immune-cell population in the tumor microenvironment (TME) of non-small-cell lung cancer (NSCLC). In this context, some of the neutrophil granule components have been proposed to contribute to tumor proliferation, angiogenesis and metastasis. Moreover, an impaired function and proliferation of lymphocytes has been linked to the action of neutrophils in the TME. However, few is known regarding the effects of MPO on NSCLC development.
Methods: *In vivo*: MPO knockout (C57/B6-J $MPO^{-/-}$; MPO-KO) and wild-type (WT) mice were subcutaneously inoculated into the flank with mouse cancer cell lines. Anti-mouse-CD8 antibody was administered to some tumor-bearing mice in order to deplete $CD8^+$ T cells. Tumor growth was monitored. Mice were sacrificed, tumors were collected, weighed and measured. Single-cell suspensions were obtained from the tumors and flow-cytometry staining of immune populations was performed. *In vitro*: A549 human lung adeno-carcinoma cells were treated with MPO, and MPO subcellular localization, cancer cell proliferation and apoptosis were investigated. Peripheral blood mononuclear cells were isolated from human blood, and T cells were enriched using a commercial kit. T cells were treated with MPO, and T cell proliferation and activation were explored. Cellular localization of MPO in T cells was also investigated.
Results: So far, we have found convincing evidence for MPO acting in favor of tumor development. *In vivo*, MPO-KO mice displayed smaller tumors in comparison to the WT littermates. Remarkably, the analysis of the TME revealed an increased number of different lymphoid populations in the $MPO^{-/-}$ mice when compared to WT mice. $CD8^+$ T cell depletion reversed the reduction of the tumor size in the MPO-KO mice. *In vitro*, MPO was able to bind and internalize in A549 cells. Furthermore, A549 cells showed increased proliferation and reduced apoptosis after MPO treatment. Phosphorylation of Akt and Erk was increased in A549 cells stimulated with MPO. Finally, MPO was able to bind and internalize in human T cells, and interestingly, the proliferation of T cells was decreased after MPO treatment.
Discussion: MPO is the major protein in granules of neutrophils and is one of the key players in neutrophil function. The current project sheds light on the role of neutrophil-derived molecules as important players in the context of tumor growth and marks MPO as an enzyme within the TME that impacts NSCLC development. Further studies are needed to understand the functional significance of MPO localization in the cytoplasm and nucleus of cancer cells and T cells. Moreover, the use of specific MPO inhibitors *in vivo* is necessary in order to implement a therapeutic approach. Our findings suggest that MPO may play a role in the development of lung cancer either by regulating cancer cell function or by influencing immune-cell behavior.

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