Progression of head and neck cancer is associated with elevated neutrophil extracellular traps formation by circulating neutrophils

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Neutrophil extracellular traps (NETs) represent web-like structures consisting of externalized nuclear and mitochondrial DNA decorated with granule proteins. NETs were discovered as structures responsible for distant trapping and killing of bacteria. However, there are also undesirable effects of NETosis during carcinogenesis; such as facilitating of metastasis by anchoring circulating tumor cells to the endothelium. Importantly, tumor cells are able to support this process by expressing multiple neutrophil activating factors, such as G-CSF.

Since neutrophils are known to negatively influence the course of head-and-neck cancer (HNC), as their increased numbers are associated with adverse patient prognosis, we addressed changes in neutrophil activity during HNC progression. To this end we assessed NETs production by isolated circulating neutrophils of head and neck cancer (HNC) patients. Percentage of NET-positive neutrophils and the mean area of NETs were estimated in HNC patient specimen (n=37) versus healthy donors (n=10). It was correlated with tumor stage, lymph node metastatic load and the expression of tumor derived factors.

While there were no significant differences in spontaneous NETosis, bacteria-stimulated NET release was significantly elevated in T1-T2 and N0-N2 stages, compared to healthy controls. Interestingly, NETosis decreased in advanced cancer (T3-4, N3). Of note, we also observed a strong expression of G-CSF by tumor tissue and a positive correlation between G-CSF levels and NETosis. This is in agreement with our observation that G-CSF stimulates NETs formation in vitro. Additionally, we analyzed the expression of CD11b, the component of beta 2 integrin, which mediates human neutrophil adhesion and migration, as well as interactions between neutrophils and tumor cells. CD11b was up-regulated on blood neutrophils in HNC T2-T3 stage and its expression correlated with G-CSF levels released by tumor tissue.

Altogether, based on the above results we suggest that NETosis is significantly elevated in patients prone to lymph nodes metastasis and could be used as a biomarker predicting metastatic spread in HNC. Therapeutic disruption of NET formation or neutrophilic adhesion may offer new roads for treatment of HNC patients in order to prevent metastasis.

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