Institutionen för klinisk vetenskap, intervention och teknik
Enheten för öron-, näs- och halssjukdomar

Pattern-Recognition Receptors and Neutrophils in Cancer Inflammation

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ABSTRACT

Chronic inflammation, induced by the use of tobacco and alcohol, or caused by infections has long been suggested to constitute a risk factor for head and neck squamous cell carcinoma (HNSCC). The innate immunity is the first line of defense against pathogens, comprising physical and chemical barriers, anti-microbial peptides, pattern-recognition receptors (PRRs) as well as different kinds of cells, including neutrophils. Among the PRRs, Toll-like receptors (TLRs) and Nucleotide oligomerization domain (Nod)-like receptors (NLRs) have gained much attention. They both recognize viruses and bacteria. In addition to their protective role against infections, accumulating evidence suggests a role for these receptors in cancer. Neutrophils are among the first cells to migrate into an inflamed tissue, and their role in various infections is well described. Several studies have demonstrated anti-tumor activities of these cells, but they are also believed to have a tumor-promoting role. Recent data indicate the existence of three distinct neutrophil subsets, $CD16^{dim}$ $CD62L^{high}$, $CD16^{high}$ $CD62L^{high}$, and $CD16^{high}$ $CD62L^{dim}$ cells, with diverse roles in infection, inflammation and cancer. The overall aim with this thesis was to investigate the potential role of PRRs and neutrophils in HNSCC.

The thesis demonstrated that the HNSCC cells exhibited high levels of TLR2, TLR3, and TLR5, and a diverse NLR expression. Stimulation of TLR2, TLR3, TLR5, and Nod1 induced a robust inflammatory response and cell death in HNSCC cells that differed from what was seen in corresponding healthy epithelial cells. Following PRR stimulation the cancer cells up-regulated their expression of ICAM-1, and TLR activation increased the secretion of IL-1β, IL-6, and IL-8. In contrast, Nod1 enhanced the production of G-CSF and GM-CSF in HNSCC cells. In addition, the TLRs also affected the survival of the malignant cells. Altogether, this strengthens the suggestion that PRRs might mediate receptor specific tumor effects that can be either anti- or pro-tumorigenic. In the present study of HNSCC, TLRs induced an anti-tumorigenic response, whereas Nod1 activation caused pro-tumorigenic effects.

Generally, HNSCC patients had a higher level of leukocytes and specifically more neutrophils in blood than healthy controls. Consequently, the neutrophil/lymphocyte ratio was high in the cancer patients, and a high ratio predicted worse prognosis. The three different neutrophil subsets mentioned above were found in the circulation of patients with HNSCC. The cancer patients exhibited a higher percentage of $CD16^{high}$ $CD62L^{dim}$ cells than the healthy controls. Among the HNSCC patients, individuals with a high percentage of $CD16^{high}$ $CD62L^{dim}$ neutrophils had a better outcome. In addition, the $CD16^{high}$ $CD62L^{dim}$ cells represented the most active neutrophil phenotype. Hence, it might be that these activated neutrophils have anti-tumorigenic properties, and therefore are more favorable for the survival of the HNSCC patients. Altogether this emphasizes the beneficence of having an ongoing process of neutrophil recruitment and activation in patients with HNSCC.

Patients with allergic rhinitis (AR) and HNSCC were found to exhibit distinct immunological reactions. The allergic patients exhibited enhanced serum levels of both Th1 and Th2 cytokines. The same increase was also seen in supernatants from their cultured PBMC. In contrast, HNSCC patients had an increase in serum level of cytokines reflecting an innate immune reaction. PMN isolated from these patients showed a generally increased basal activation, and responded strongly to TLR stimulation. Further, tumor biopsies from HNSCC patients displayed a higher Nod2 mRNA expression than nasal biopsies from healthy controls and AR patients outside and during pollen season. All in all, the immune reaction among the allergic patients had an adaptive character with an enhanced T cell activity, whereas the immune reaction of the HNSCC patients was dominated by an innate immune response with suppressed T cells. It is therefore tempting to propose that the enhanced systemic adaptive immune response seen among patients with AR might protect against development of HNSCC.

In summary, this thesis demonstrates a receptor specific expression and function of PRRs in HNSCC. It also reveals that the inflammation in HNSCC is dominated by innate immune activities, and that recruitment and activation of neutrophils is important for the survival of these patients. Consequently, the ability to muster a proper inflammatory reaction might be vital for the defense and survival in patient with HNSCC.

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