Toll-like receptor 5 and the emerging role of bacteria in carcinogenesis

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Bacteria play a prominent role in immunoregulation but also can cause local and systemic inflammation. Chronic inflammation as well as certain bacteria such as Helicobacter pylori have been shown to promote oncogenesis. The oral mucosa and gastrointestinal tract are highly colonized by commensal bacteria, helping to regulate the immune system, preventing allergies and fighting off virulent bacteria. The discrimination between commensal and pathogenic bacteria is difficult, especially if the species does not cause short-term problems but facilitates carcinogenesis over long periods of time. Among thousands of different bacterial species constituting the oral flora, there are only a few with known healthy or pathogenic effects.

Toll-like receptor 5 (TLR5) is a pattern recognition receptor recognizing flagellin, a component of bacterial flagella. TLR5 is expressed by multiple cells of the immune system, a setting in which it stimulates inflammatory responses, but also by epithelial and cancer cells. In malignant cells, TLR5 not only promotes inflammatory responses but also stimulates invasion, migration, and chemokine secretion.

We have recently sought to evaluate the significance of TLR5 in oral carcinoma by assessing TLR5 expression in a cohort of 119 oral tongue squamous cell carcinoma (OTSCC) patients. We found out that the expression of TLR5 was more abundant and widespread in cancer cells than in the adjacent healthy epithelium, where TLR5 is mainly expressed by squamous cells of the basal layer. Importantly, TLR5 expression levels predicted patient prognosis. Multivariate analyses showed that high TLR5 levels were a predictor of cancer-related death (hazard ratio = -3.5) as well as cancer recurrence (hazard ratio = -4.4).

Our results indicate that TLR5 plays a role in the progression of oral carcinoma and favors a contribution for TLR5 in oral carcinogenesis as well. As a poor oral hygiene is a known risk factor for OTSCC and no endogenous ligands for TLR5 are known to date, our findings point to a bacterial activation of TLR5 exerting pathophysiologically relevant effects. A few bacterial species including Streptococcus mitis, Prevotella melaninogenica and Capnocytophaga gingivalis have been associated with oral cancer, but their actual role in the oncogenic process remain unknown.

During carcinogenesis, the expression pattern of TLR5 and other TLRs changes from a basolateral to diffuse, and in layered epithelia expression extends to the upper cell layers. Such an abnormal expression of TLR5 has been proposed as a biomarker for epithelial dysplasia in gastric and cervical epithelia. Interestingly, these changes lead to a situation in which TLR5 is expressed at the luminal surface, increasing the possibility for the recognition of bacterial components. Several reports on the effects of TLR5 activation on different cancers have been published, with contradictory results. Indeed, TLR5 has been suggested to exert antitumor effects as well as to promote invasiveness. The effects of TLR5 activation seem to vary with cancer type and anatomical localization, similar to what reported for TLR9.

In general, TLRs appear to operate in two different ways, depending on the cell type. Cancer cells are more aggressive in response to TLR activation, whereas immune cells often respond to TLR agonist by exerting antitumor effects. Increased TLR expression levels and the structural aberrations that characterize malignant epithelia, such as the loss of cell polarity and abnormal intercellular junctions, might allow bacteria and their components to activate TLRs, hence contributing to disease progression. Other endogenous and exogenous TLR ligands as well as the existence of functionally different TLR isoforms further add to the complexity of this setting. Dying cells (be they malignant or not) release DNA fragments, heat-shock proteins and several other intracellular factors that are sensed by both immune cells and living cancer cells, hence mediating...
In summary, we demonstrated a prognostic value for TLR5 in OTSCC patients. Hence, TLR5 expression levels might constitute a useful tool to recognize OTSCC patients at increased risk for recurrence and death, especially in the early stages of the disease. In particular, TLR5 could be detected by immunohistochemistry in primary biopsies to help clinicians in the decision on whether or not to proceed with extensive resection, neck dissection or start post-operative radio- or chemotherapy.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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