Causes and pathology of mucositis

Defention: One of the most debilitating side effects of radiotherapy and chemotherapy treatment. It is characterized by both inflammation and cell loss in the epithelial barrier. Mucositis is a very complex condition: it develops as a series of dynamic interactions that begin in the epithelium but in a later stage involves other tissue mucosal components like the endothelium, extracellular matrix and connective tissue. It is a frequent reason to postpone chemotherapy treatment ultimately leading towards a higher mortality in cancer patients.

The pathobiology can be described in five stages: initiation, message generation, signal amplification, ulceration and healing.

5 stages:

Initiation phase: The initiation phase follows immediately after exposure to radiation or chemotherapy. The treatments cause the production of reactive oxygen species (ROS). These are free radicals that cause DNA strands in epithelium cells to break. Thus arising reversible and irreversible DNA damage.

Message generation phase: In the message generation phase different transcription factors are activated. The most important is nuclear factor-kappa B (NF-κB), this is a regulatory molecule that controls nearly 200 genes of which that encode pro-inflammatory cytokines and cell adhesion molecules. The increase in synthesis of cytokines and other enzymes causes an increase in apoptosis of epithelial cells and fibroblasts.

Signaling and amplification phase: One of the pro -inflammatory cytokines produced is tumor necrosis factor alpha (TNF-α), this molecule damages the cells but also increases the activity of NF-κB. With as result a positive feedback loop that causes amplification of injury that also continues after the cancer therapy. Until now there is little manifestation of symptoms.

Ulceration phase: The real problems begin when there is penetration through the epithelium into the submucosa. There is the beginning of an ulcer and on the ulcer surface oral bacteria colonize. The bacteria produce toxins and inflammatory cytokines in reaction with macrophages. This phase is responsible for the most symptoms occurring in mucositis. The ulceration can result in complications like bacteremia (infection of blood with bacteria) and sepsis. Ulceration associated with mucositis also increases the risk for viridans streptococcal bacteremia, septicemia and systematic infection.

Healing phase: Healing can occur spontaneous or can be improved by therapy. Epithelial cells which are under control of the extracellular matrix move, migrate, grow and differentiate to form a wound.

This cycle of stages can be repeated several times in different sites on the oral mucosa throughout the course of therapy.

The role of bacteria in oral mucositis

According to this five phase model the oral microbiota play no role in the pathobiology of mucositis. However research has implicated a role for the commensal microbiota in several inflammatory diseases like inflammatory bowel disease. (as we saw in the previous lesson about crohn disease). It’s

likely that the commensal bacteria also play a role in this inflammatory disease : mucositis. Commensal microbiota might have a beneficial effect on the development of oral mucositis, they might offer protection against its development. There are five pathways in the development of mucositis that are potentially influenced by the commensal oral microbiota:

Influencing the inflammatory process

The resident bacteria cause a constant state of low grade inflammation. They guarantee the presence of ligands for TLR such as peptidoglycaan and LPS. This ensures an activation of the downstream signaling pathways resulting in a low grade inflammation. Paradoxically, commensal bacteria are also capable to suppress more severe inflammatory responses. Multiple bacteria are capable of decreasing NFkB activation, resulting in less production of inflammatory cytokines. This can be done by regulating the expression of TLR. They may secrete substances that induce the production of anti-inflammatory cytokines. Also SCFA produced by the oral microbiota can attenuate the inflammation.

Influencing the permeability of the mucosa

The permeability of the oral mucosa increases after chemotherapy treatment as lots of cells are damaged in the third en fourth phase of the process. However, the resident microbiota also influence the permeability. Some bacteria are associated with the expression of more proteins that form tight junctions between the cells. Another factor that might contributes to this effect is the bacterial induction of heat shock proteins. HPS’s preserve the viability of the epithelial cells in stress conditions. (Proteins formed in stress

situations such as high temperature or irradiation) Also SCFA have a positive effect on the viability of the epithelial cell.

Influencing the composition of the mucus layer

The composition of the mucus layer is important in the protection against bacterial infection and inflammation. The commensal bacteria play an important role in the maintenance of the mucus layer. The absence of oral microbiota is associated with with a decrease in goblet cells and the size of these goblet cells. Also the thickness of the layer is decreased in animals devoid of microbiota. The genes encoding mucins are regulated by bacteria and their products. Besides interaction with the genes the also interfere with the glycosyltransferases, enzymes that are responsible for the length of the carbohydrate side chains of the mucins. And thereby influencing the strength of the mucus layer. The stronger the mucus layer the stronger the barrier against translocation of bacteria in the blood. Thereby possibly attenuating the inflammation in the ulceration phase.

Influencing epithelial repair

The commensal bacteria stimulate epithelial repair, they have an influence on the healing phase of mucositis. In germ-free animals the mitotic rate and the cell turnover of epithelial cells are lower as compared to normally colonized animals. The bacterial induction of NFkB not only controls the low inflammatory state of the mucosa but also stimulates the repair of damaged epithelial cells. Also butyrate plays a role, it stimulates the migration of epithelial cells thereby enhancing the healing of the mucosa.

Influencing the production and release of immuno effector molecules

By influencing the expression and release of immuno effector molecules, the commensal intestinal microbiota regulates it self and maintain homeostasis in the mouth. For example when the contact between microbiota and epithelium suddenly increases the expression of lectins increases. This protein has antimicrobial activity and limits bacterial translocation. Another effector molecule influenced by the resident microbiota is IgA. Not only living bacteria but also their products are capable of up regulating immuno effector molecules. For example , SCFA such as butyrate regulate the production of cathelicidines , which have a broad antibacterial activity.

Most studies hat investigate the role of bacteria in disease have focused on inflammatory bowel disease, which is caused by a chronic inflammatory process instead of the acute damage induced by chemotherapeutics and irradiation. It has been shown that chemotherapy treatment is associated with a changed oral flora. Restoring the changed oral flora may decrease the morbidity and mortality of cancer patients as the oral microbiota have a beneficial effect. Further research is needed whether the role of the commensal bacteria should be incorporated in the five phase model and to show the relevance of restoring the microbial imbalance in the mouth caused by the irradiation and chemotherapeutics, thereby possibly decreasing the degree of oral mucositis. Probiotics could play a role in restoring the microbial homeostasis in the mouth.