PERSPECTIVES

Oral microbiota: An overlooked etiology for chemotherapy-induced oral mucositis?

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Introduction

Oral mucositis, characterized by inflammatory response and cell loss in the epithelial cells lining of the oral cavity, is one of the most debilitating adverse effects of chemotherapy. In patients undergoing high-dose myeloablative therapies, the incidence rate of oral mucositis is almost 100%, and in cancer patients undergoing standard-dose chemotherapy the rate is 40–60%. Chemotherapeutic agents with pronounced stomatotoxic effects are listed in Table 1. Pain, odynophagia, dysgesia, and subsequent malnutrition of oral mucositis have become a common reason for decreasing the dosages of antineoplastic agents, necessitating deference or cessation of antineoplastic treatments, and preventing patients from optimal chemotherapy regimens, ultimately leading to higher mortality in cancer patients. In addition, a vast variety of microorganisms including bacteria, fungi, and viruses in the oral cavity may enter the bloodstream because of the loss of mucosal integrity, leading to systemic infections that interrupt antineoplastic treatments, or even jeopardize patients’ lives. Historically, chemotherapy-induced mucositis was thought to occur solely because of the basal cell damage of the epithelium when drugs permeate into these cells via the submucosal blood supply. Recent advances in understanding its pathological mechanism indicate that it is the consequence of a series of dynamic and interactive biological events involving the epithelia and submucosa in response to stomatotoxic agents. A number of factors such as treatment regimens, duration of treatment, dose intensity, previous mucosatoxic treatments, the quality and quantity of saliva, and lack of detoxification enzyme activity, influence an individual’s risk of mucositis. The five-phase pathobiological model of mucositis proposed by Sonis includes: (1) the initiation phase characterized by the formation of reactive oxygen species caused by chemotherapy agents, which activates nuclear factor kappa B; (2) the induction of messenger molecules such as interleukin 6 and tumor necrosis factor alpha during the primary damage response phase, which causes tissue inflammation and apoptosis; (3) more inflammation and apoptosis during the signal amplification phase as a consequence of the amplification of messenger molecules; (4) loss of mucosal integrity due to apoptosis during the ulcerative phase, thereby promoting superficial bacterial translocation; and (5) a self-resolving healing phase, characterized by cell proliferation and differentiation. According to this model, inflammation together with apoptosis lead to the loss of integrity of the mucosal barrier, thereby promoting bacterial translocation. The oral microbiota per se is thought to play a small role in the initiation of oral mucositis. However, therapy options based on this pathobiological model are not satisfactory. Chemotherapy-induced oral mucositis is still a therapeutic challenge, necessitating in-depth etiological studies that may lead to a...
better treatment. The correlation of the ecological shift of gut microbiota with intestinal mucositis among cancer patients undergoing chemotherapy has been recently reported. A disturbed balance of intestinal microbiota featuring a 100-fold increase of potentially pathogenic aerobic enterococci and 10,000-fold decrease of anaerobic bacteria has been discovered in patients with leukemia who are vulnerable to intestinal mucositis. \(^3\) van Vliet et al. \(^4\) have proposed that bacteria may play a dynamic role in the development of chemotherapy-induced mucosal injury within small intestine, by influencing: (1) the inflammatory progress and oxidative stress, (2) the constitution of the mucus layer, (3) intestinal permeability, (4) the expression and discharge of immune effector molecules, and (5) the resistance toward harmful stimuli and epithelial repair ability. In addition, promising results have been obtained from the therapeutic use of probiotics to alleviate chemotherapy-induced intestinal mucositis in both animal model and clinical trials. All these findings strongly indicate the involvement of microbial homeostasis in the pathogenesis of chemotherapy-induced mucositis in the intestine. However, the correlation of oral microbial homeostasis and chemotherapy-induced oral mucositis is not well documented.

**Hypothesis**

We hypothesized that chemotherapy may inhibit the commensal bacteria within the oral cavity and induce an ecological shift of oral microbiota toward a community predominated by Gram-negative anaerobes exhibiting high virulence phenotype, thus initiating a cascade of inflammatory processes involving the development of oral mucositis.

**Evaluation of the hypothesis**

**Commensal bacteria and oral homeostasis**

The human oral cavity is a complex ecosystem characterized by the presence of a wide variety of bacterial colonizers that coexist with each other and thrive in a dynamic environment. Emerging evidence suggests that oral microbiota plays an important role in stimulating mucosal epithelial cells and maintaining the mucosal barrier that contributes to host defense. *Streptococcus salivarius* K12, a commensal Gram-positive microbe, can stimulate an anti-inflammatory response in oral epithelial cells and modulate genes associated with homeostasis. \(^5\) The cell wall extract of an oral commensal mirobe, *Fusobacterium nucleatum*, but not the more pathogenic *Porphyromonas gingivalis*, can induce the production of human β-defensin 2, contributing to innate immunity and host defense. \(^6\) Preliminary data obtained from culture-based methodologies have shown that antineoplastic agents can affect oral microbial composition. Cytotoxic antineoplastic agents can therefore compromise oral mucosal immunity, which can lead to decreased Secretory Immunoglobulin A (SIgA) secretion, salivary dysfunction, decreased salivary antimicrobial properties, and damage of the mucosal barrier lining the oral mucosa, further disrupting eubiosis of oral microbiota. Therefore, we believe that oral mucositis may occur when oral commensal bacteria are unable to offer protection with the disruption of the ecological balance during chemotherapy.

**Pathways activated by disturbed oral microbiota during mucositis**

On the molecular level, the disturbed oral microbiota could be involved in the inflammatory process of chemotherapy-induced mucositis through two groups of receptors: Toll-like receptors (TLRs) and nucleotide oligomerization domain (NOD)-like receptors (NLRs). TLRs, which exist at the outer membrane of the epithelium or intracellular vesicles, function as pattern recognition receptors that recognize a wide range of microbial pathogens. Activation of TLRs by recognition of microbial components, such as peptidoglycan, lipopolysaccharide, bacterial DNA, and protein flagellin, triggers a cascade of cellular signals resulting in the activation of nuclear factor kappa B, which leads to inflammatory gene expression and development of the inflammatory response of mucosa. \(^7\) Moreover, after binding with TLRs, bacteria are processed there and bacterial parts are transported within cells, and then bind to NLRs, which are a newfound group of intracellular cytosolic sensors playing a crucial role in the regulation of the host inflammatory response. The best studied is NLRP3 (NLR family, pyrin domain-containing 3), which recruits—through the adaptor protein ASC—caspase-1 forming into a multiprotein complex named the inflammasome. Once activated, caspase-1 processes proinflammatory cytokines (such as pro-IL-18 and pro-IL-1b) to their active and secreted forms, thus regulating inflammatory response. \(^8\) Therefore, TLRs, NLRs and their downstream pathways may be the potential target of oral microbiota to initiate mucosa inflammation among cancer patients undergoing chemotherapy.

**Implication of the hypothesis**

Further research is warranted to clarify the pattern of ecological shift of oral microbiota during chemotherapy and its relationship with oral mucositis using high-throughput metagenomic sequencing and global transcriptomic profiling. Once the involvement of microbial ecological shift in the pathogenesis of chemotherapy-induced oral mucositis is elucidated, it may contribute to the development of effective antimicrobial agents to specifically inhibit emerging pathogens or to restore the homeostasis of oral cavity. A specifically targeted antimicrobial peptide has been developed and proven to effectively kill *Streptococcus mutans* while leaving other bacteria unaffected. Thus, the development of narrow-spectrum agents targeting the specific pathogens of oral...
mucositis is possible. Because the use of whole bacteria as probiotics to restore oral dysbiosis could cause severe infections in immunocompromised patients, the use of bacterial parts to attenuate oral mucositis might also be promising. Further in vitro and in vivo experiments are needed to validate these potential measures.

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References