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Review

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The Association Between Oral Anaerobic Bacteria and Pancreatic Cancer

Mesut Ogrendik

Abstract

Reports have shown increased positive correlations with the salivary microbiota and pancreatic carcinogenesis. A European study showed that high levels of *Porphyromonas gingivalis* were correlated with periodontium damage and were associated with a risk of pancreatic cancer (two-fold). A recent study, using oral mouthwash samples (n = 361 with pancreatic adenocarcinoma), determined that the presence of *P. gingivalis* and *Aggregatibacter actinomycetemcomitans* along with *Fusobacteria* and *Leptotrichia* were a risk factor for pancreatic cancer. The link between pancreatic cancer and periodontitis has been documented. Interestingly, periodontitis presents with inflammation and microbial dysbiosis, both of which have been characterized in pancreatic cancer. This review highlights multiple roles in which oral anaerobic bacteria can spread to the pancreas and contribute to pancreatic cancer.

Keywords: Pancreatic cancer; Oral bacteria; Periodontitis

Introduction

Pancreatic cancer is an intractable malignancy and is the third leading contributor to global cancer mortality in industrialized countries and the USA [1]. A large prospective study conducted in the USA has reported a risk of periodontal disease in pancreatic cancer of approximately 31% [2].

Periodontitis, an inflammatory disease, can weaken the gums resulting in tooth loss due to gingival infection, which extends to gingival connective tissue, periodontal ligaments, and alveolar bone [3]. In these diseases, the primary etiologic factors are pathogenic microorganisms comprising a complex polysaccharide matrix in the form of a biofilm [3]. Periodontopathogens and their toxins are important in the initiation and development of periodontal diseases with chronic and infectious features as well as host defense [3].

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Department of Physical Medicine and Rehabilitation, Izmir Democracy University, Seyfi Demirsoy Training and Research Hospital, Buca, Izmir, Turkey.
Email: mogrendik@hotmail.com

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The host response protects periodontal tissues against local microbial attacks and prevents the spread of pathogenic microorganisms in the tissue [3]. However, the host response can also damage surrounding cells and the extracellular matrix, leading to damage and loss of gums, periodontal ligaments, cementum, and alveolar bone [3].

This review highlights multiple roles by which oral anaerobic bacteria can spread to the pancreas and contribute to pancreatic cancer.

Periodontal Pathogens and Pancreatic Cancer

Periodontal disease is a group of disorders that affect the supporting tissues of the teeth [3]. The predominant microflora found in disease differs from that in health, but there is no single or unique pathogen. Most of the bacteria associated with the disease are Gram-negative and obligately anaerobic, except for localized juvenile periodontitis, where the microflora is mainly capnophilic [3]. Although the microflora is diverse, certain species are commonly found at sites that undergo tissue breakdown; these include *Porphyromonas gingivalis, Prevotella intermedia, Aggregatibacter actinomycetemcomitans, Bacteroides forsythus, Campylobacter rectus, Fusobacterium nucleatum, Eubacterium* spp., and *Spirochaetes* [3].

Many of these species are highly proteolytic and degrade host tissues and/or components of host defenses, including key regulatory proteins of the inflammatory response [3]. Bacterial invasion of tissues is rare, except in some acute conditions such as acute necrotizing ulcerative gingivitis and localized juvenile periodontitis and in more advanced stages of disease [3]. Acute forms of periodontal disease may also be due to abnormalities in host defenses; other risk factors include diabetes mellitus and smoking. Tissue destruction is generally mediated by bacterial cell surface proteases and extracellular cytotoxic compounds [3]. Organisms can evade or subvert the host defenses by the action of specific proteases and leukotoxin production or by the presence of a capsule [3]. Periodontal diseases involve tissue destruction directly by bacterial enzymes and indirectly as a consequence of the host inflammatory response ("bystander effect") [3]. Periodontal diseases may also act as risk factors for more serious medical conditions, including preterm, low birth weight babies, and cardiovascular disease [3]. Treatment and prevention of periodontal disease involves good oral hygiene, which may be augmented by the use of antimicrobial agents [3].

Periodontal disease is caused by several other causes than

periodontal infection [3]. These causes include smoking, pregnancy, diabetes mellitus, genetic diseases, drugs, and immune suppressive diseases.

A recent study, using oral mouthwash samples (n = 361 with pancreatic adenocarcinoma), determined that the presence of *P. gingivalis* and *A. actinomycetemcomitans,* along with *Fusobacteria* and *Leptotrichia,* was a risk factor for pancreatic cancer [4]. These data concluded that the presence of *P. gingivalis* increased cancer development by 59%, while *A. actinomycetemcomitans* increased risk by 50%, suggesting that oral microbial dysbiosis precedes the development of cancer [4].

A European study (n = 404) showed that high levels of *P. gingivalis* were correlated with periodontium damage and were associated with a risk of pancreatic cancer (two-fold) [5]. In addition, this report showed that patients with increased antibody levels had a 45% lower possibility of pancreatic cancer compared to controls with low antibodies. This is the first study to demonstrate the relationship between oral bacterial antibodies and pancreatic cancer.

P. gingivalis and Pancreatic Cancer Risk

Periodontitis has been associated with a localized and destructive immune response with multiple systemic effects [3]. Ahn et al prospectively examined clinically detected periodontitis and immune response to *P. gingivalis* [6]. According to the NHANES [7], *P. gingivalis* was associated with mortality from orodigestive (OD) cancer. Moderate or severe periodontitis was correlated with increased mortality rates in patients with OD cancer (relative risk (RR) = 2.28, 95% confidence interval (CI) = 1.17 - 4.45). Mortality was also higher with increased severity of periodontal disease (P = 0.01). The mortality rate due to periodontitis was high in colorectal cancer (RR = 3.58; 95% CI = 0.15 - 11.16) and pancreatic cancer (RR = 4.56; 95% CI = 0.93 - 222.29).

Higher antisera (IgG) against *P. gingivalis* were generally associated with higher mortality in OD cancer (P = 0.06); excess OD mortality associated with *P. gingivalis* was also observed in control patients who did not show open periodontal disease (RR = 2.25; 95% CI = 1.23 - 4.14). Mortality rates from OD cancer were associated with *P. gingivalis* without the presence of periodontitis and PD.

P. gingivalis and Carcinogenesis

In a new murine model of periodontitis-induced oral tumorigenesis, squamous cancer cells and increased interleukin (IL)-6 signaling were shown to activate STAT3 phosphorylation [8]. This, in turn, stimulated the effectors of oral squamous cell carcinoma (OSCC) to enhance growth and cellular invasion. Data were consistent with multiple reports suggesting pro-tumor activity of IL-6 signaling and STAT3 phosphorylation [9, 10]. IL-6 production has been shown to be enhanced by *P. gingivalis* in epithelial cells [9, 11]. Activation of JAK2 and GSK3 beta-pathways was observed by the following administration of this bacteria.

Binder Gallimidi et al reported that *P. gingivalis* and *F. nucleatum* both induce tumorigenesis through activation of Toll-like receptors in oral epithelial cells, which induced IL-6 [8]. Furthermore, oral pathogens have been shown to induce OSCC proliferation, as well as cyclin D1, matrix metalloproteinase (MMP)-9 and heparanase expression, all of which have been associated with tumorigenesis 8]. Geng et al exposed human oral epithelial cells to *P. gingivalis* for 5 - 23 weeks [12]. Continuous exposure resulted in increased cellular proliferation and increased cells in phase S of the cell cycle.

Peptidylarginine Deiminases (PADs) and Protein Citrullination in Cancer

The red complex consists of *Tannerella forsythia, P. gingivalis*, and *Treponema denticola,* which has arginine-specific proteases (PADs) and plays a role in severe periodontal disease [3]. *P. gingivalis* also has a lysine-specific protease [3]. This protease has been shown to alter host and bacterial proteins through the conversion of L-arginine to L-citrulline [13-16]. Protein citrullination releases host inflammatory cytokines by altering the 3D structural configuration and function of the protein [17, 18]. The host also has sources of citrullination through genes encoding the five calcium-linked enzyme families PAD1, 2, 3, 4/5, and 6. These are not the same as PPAD.

The host PADs are associated with a variety of human and animal tumors [19-22]. Thus, Kholia et al documented that the expression levels of PAD2/4 and cytoskeletal actin were increased by microvesiculates during the induction of PC3 cells, which are important in cancer progression [21]. Pharmacological inhibition of PAD significantly decreased microgranule release and abolished cytoskeletal actin release. PAD4 [19, 23, 24] and PAD2 are overexpressed in various types of invasive carcinoma and appear to be involved in tumor progression. PAD inhibitors have been shown to suppress inflammatory symptoms and tumor progression [22].

PAD4 has been found to bind an inhibitor of growth 4 (ING4), another tumor suppressor protein that is known to bind p53, followed by citrulline [25]. Citrullination of ING4 driven by PAD4 in the nuclear localization sequence region prevented binding of p53 to ING4, suppressed p53 acetylation and, later, inhibited downstream p21 expression [25].

P. gingivalis and the Cell Cycle

Bacterial infection can impact host cell cycle progression as a survival mechanism.

P. gingivalis has been shown to change protein phosphorylation involved in the eukaryotic cell cycle including p53 and P13K [26]. Increased proliferation of human gingival epithelial cells infected by *P. gingivalis* increased the number of cells in phase S. Furthermore, Pan et al showed that *P. gingivalis* influences the transition of the cell cycle G1/S of human gingival epithelial cells, which expresses the rearrangement of cyclin D/E [27]. The impact of bacteria that enhance cell

proliferation to the carcinogen should not be disregarded; the latter is a long-lasting multistage and multifactor process.

P. gingivalis inhibits apoptosis through rearrangement of Bcl-2 and subregulation of the pro-apoptotic BAD protein [28]. Ogrendik postulated that bacterial PAD enzymes cause gene mutations of p53 and K-ras, which can contribute to pancreatic tumors when secreted by oral bacterial flora [29, 30].

Conclusions

Periodontal disease is positively associated with a risk of pancreatic cancer [31]. Oral cancer cells infected with *P. gingivalis* for a long period exhibit resistance to Taxol and have higher metastatic potential [32]. *P. gingivalis* causes this result by activating the intracellular domain of the notch intracellular domain 1 [32]. *P. gingivalis* increases the migratory and invasive capacities of OSCC cells, as well as the release of CD44 and CD133 [33]. Furthermore, it causes heightened MMP-1 and MMP-10 induced by IL-8 release [33]. In conclusion, periodontal pathogens can spread to the pancreas and cause pancreatic carcinogenesis.

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None to declare.

Conflict of Interest

None to declare.

Data Availability

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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