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Mini-Review

Periodontal Pathogens in the Etiology of Pancreatic Cancer

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Keywords
Etiology · Pancreatic cancer · Periodontal pathogens

Abstract
Background: Pancreatic cancer is the fourth leading cause of cancer-related deaths worldwide. Chronic pancreatitis is frequently observed in patients with pancreatic cancer, and a significant relationship between orodigestive cancer-related deaths and chronic periodontitis has been detected. *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*, collectively called the Red complex, are the major pathogens responsible for chronic periodontitis and secrete peptidylarginine deiminase. Anti-*P. gingivalis* antibodies titers are higher in pancreatic cancer patients than in healthy subjects. ***Summary:*** This review examines the association between oral bacteria and the etiology of pancreatic cancer. ***Key Message:*** High rates of tumor suppressor gene *p53* mutations, particularly *p53* arginine mutations, were detected in pancreatic cancer patients. *K-ras* arginine mutations were detected in patients with pancreatic cancer. Oral bacteria peptidylarginine deiminases might lead to the *p53* and *K-ras* point mutations by degrading arginine. ***Practical Implications:*** Oral bacteria are likely to be responsible for the development of pancreatic cancer. If this hypothesis is true, it may reveal the real cause of pancreatic cancer, which is a fatal disease.

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths worldwide [1] and causes approximately 8,000 deaths in the United Kingdom every year [2]. The rate of this cancer has been increasing in Western countries [3]. Chronic pancreatitis is frequently observed in patients with pancreatic cancer [4], and a significant relationship between orodigestive cancer-related deaths and chronic periodontitis has been detected [5].

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Periodontal diseases are a group of disorders that affect the supporting tissues of the teeth. Periodontal diseases are common; for example, in a national survey in the United Kingdom, 79% of dentate adults had bleeding gums, 88% had calculus, and 69% had periodontal pockets, including 10% with deep pockets [6].

In periodontal diseases, the junctional epithelial tissue at the base of the gingival crevice migrates down the root of the tooth to form a periodontal pocket [6]. This movement is a direct result of the microorganisms themselves and the indirect but potentially damaging side effects of the host's inflammatory response to plaque accumulation. Individuals with periodontal disease have different predominant microflora than healthy individuals, but there is no single or unique pathogen associated with the disease. Most are gram-negative and obligately anaerobic, except for capnophilic microflora which are associated with localized juvenile periodontitis [6]. Although the microflora in periodontal disease are diverse, certain species are commonly found at sites undergoing tissue breakdown, including *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, *Prevotella intermedia*, and *Treponema denticola* [6].

Among the gram-negative bacteria isolated in high numbers from sites affected by periodontal disease, *P. gingivalis* has been shown to have the greatest proteolytic activity and to be the most virulent species inoculated in animals in a simple pathogenicity test [6]. The majority of this proteolytic activity has been characterized as gingipain, an arginine-specific cysteine protease [6]. *P. gingivalis*, *T. forsythia*, and *T. denticola*, collectively called the Red complex, are the major pathogens responsible for chronic periodontitis and secrete peptidylarginine deiminase [6].

The study did not include human subjects, therefore ethical approval was not required.

Periodontal Pathogens and Pancreatic Cancer

It has been shown that the periodontal pathogens *P. gingivalis* and *Fusobacterium nucleatum* stimulate tumorigenesis and human oral tumor proliferation [7]. Michaud et al. [8] detected higher levels of antibodies formed against *P. gingivalis* in patients with pancreatic cancer than in healthy volunteers. Their multicenter study was performed on 405 pancreatic cancer cases and 416 matched controls. They observed a 2-fold increase in pancreatic cancer among individuals who had high levels (>200 ng/ml) of antibodies to the periodontal pathogen *P. gingivalis* ATTC 53978 compared with those with lower levels (≤200 ng/ml). It was the first study to examine antibodies to oral bacteria and the risk of pancreatic cancer. The findings suggest that individuals who have high levels of antibodies to *P. gingivalis* ATTC 53978 are at higher risk of pancreatic cancer.

Mutations in Pancreatic Cancer

High rates of tumor suppressor gene *p53* mutations, particularly *p53* arginine mutations, were detected in pancreatic cancer patients [9]. There is a close relationship between p53ArgPro mutations and gastrointestinal cancers, including pancreatic cancer [10].

K-ras codon 12 arginine mutations were detected in pancreatic cancer patients in one study and have been observed in others [11, 12]. Point mutations at codon 12 of the *K-ras* gene have been observed in more than 75% of pancreatic cancer patients [13]. These mutations are considered a sign of poor prognosis [14]. The GTPase-activating protein arginine finger is crucial for the interaction of Ras [15].

Conclusions

Oral bacteria peptidylarginine deiminases might lead to *p53* and *K-ras* point mutations by degrading arginine. Oral bacteria are likely to be responsible for the development of pancreatic cancer. If this hypothesis is true, it may reveal the real cause of pancreatic cancer, which is a fatal disease.

Disclosure Statement

The author declares that he has no conflict of interest. This work received no funding.

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