Institut Pasteur
Microbes and Infection 17 (2015) 473–483
www.elsevier.com/locate/micinf

Prelude to oral microbes and chronic diseases: past, present and future

Kalina R. Atanasova [a], Özlem Yilmaz [a,b,*]

[a] Department of Periodontology, University of Florida, Gainesville, FL 32610, USA
[b] Emerging Pathogens Institute, University of Florida, Gainesville, FL 32610, USA

Received 10 February 2015; accepted 10 March 2015
Available online 24 March 2015

Abstract

Associations between oral and systemic health are ancient. Oral opportunistic bacteria, particularly, *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, have recently been deviated from their traditional roles as periodontal pathogens and arguably ascended to central players based on their participations in complex co-dependent mechanisms of diverse systemic chronic diseases risk and pathogenesis, including cancers, rheumatoid-arthritis, and diabetes.

Keywords: Oral microbes; *Porphyromonas gingivalis*; *Fusobacterium nucleatum*; Cancer; Chronic diseases; Small molecule danger signaling

1. Introduction

The oral microbial communities have evolved along with *Homo sapiens* and developed together with our dietary and hygienic habits over millions of years [1]. The first documented dental procedures date back to Neolithic times only about 8000 years BC [2] and dentistry and medicine have been linked in ancient records dating back to Egyptian times approximately 4000 years BC [3]. The importance of oral health for holistic wellbeing is also not a novel concept, as ancient civilizations of the Mediterranean, for example, had already noticed that teeth problems are associated with reproduction problems in women [4], and Hippocrates treated joint pain with tooth extractions (460–377 BC). With the discovery of microorganisms, and their causative link to diseases in the early 17th and throughout 18th century, the association between oral health and oral microbiota, became even more pronounced [3]. The concept of the single-pathogen causality became fashionable among the scientific community and Robert Koch postulated the criteria to establish a causative relationship between a microbe and disease [3]. However many diseases and conditions remained unexplained by single pathogens. Moreover, with the development of the modern molecular tools the concept of the microbiome and the balance of the microbial communities that colonize the human body came to light [5,6]. Currently the links between the oral microbial consortia and their interactions with the host in the maintenance of homeostasis and in the pathogenesis of many diseases have taken center stage [6]. This more novel concept attributes the observed systemic effects not to secondary dissemination and spread of specific microorganisms and/or their toxins, but to a dysbiotic change in the constitution and inter-microbial interactions of the healthy oral microbial community, leading to an immune response from the host, locally and systemically [3].

Yet, the truth seems to lie in between. Even within the concept of the oral microbiome as a dynamic society of over 700 species of inter-communicating microorganisms, many of which still not cultivable, certain key species, such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum* have stolen the attention with their ability to modulate the balance of the microbiome and the subsequent interactions with the host mucosa and immunity [7–10]. Based on the recent

* Corresponding author. Department of Periodontology, College of Dentistry, And Emerging Pathogens Institute, University of Florida, Gainesville, FL 32610-0434, USA. Tel.: +1 (352) 273 8003.
E-mail address: oyilmaz@ufl.edu (Ö. Yilmaz).

http://dx.doi.org/10.1016/j.micinf.2015.03.007
1286-4579/

archeological findings from calcified dental plaque, giving a snapshot information of the period when hunter-gatherer societies started converting to farming of domesticated animals and plants approximately 10,000 years ago, the change in lifestyle and diet seem to have led to an explicit shift in the composition of the oral microbiota featuring increased presence of certain species, such as *P. gingivalis* [1]. This change in the microbiome also correlated with a more frequent occurrence of severe forms of periodontal disease in those populations and seems to suggest a correlation of the severity of chronic diseases of the oral cavity with the change in the environmental factors [1]. In today's urbanized human society, aside from the diet there are many other contributing factors, such as environmental pollution, climate, lifestyle and distinct health habits, which may also simultaneously influence the oral communities and have been linked with a noted increase in the frequencies of a broader array of chronic diseases [11].

Apart from the now well established role in periodontal disease, a select group of oral microbes have increasingly become associated with chronic diseases such as orodigestive cancer, rheumatoid arthritis, diabetes, and some other severe chronic diseases. These new observations have critically transformed the traditionally accepted views especially on the opportunistic chronic pathogens of the oral cavity and how those microbes may have engaged with human health and disease [12–15]. Among those microorganisms, *P. gingivalis* has frequently been linked with the potential development and/or advancement of several distinct chronic diseases and has become a much highlighted topic of research. Thus, this review will critically examine the newly started to be characterized roles of a selective number of oral microbes in cancers, rheumatoid arthritis, diabetes, and chronic inflammatory conditions of the liver, kidneys and lungs. In addition, it outlines mechanistic connections among the highly complex cellular and metabolic molecular networks that appear to be predominantly co-shared by these seemingly unrelated chronic diseases and also modulated by the specific subset of oral opportunistic pathogens (The postulated interactions are illustrated in Diagram 1).

2. Cancer and oral microbes

Although late archeological evidence suggests that cancers have existed as far back as the earliest human civilizations, the fact that cancers are relatively rare in archaic mummified remains from old civilizations worldwide (4000–400 BC) highlights that the incidence of cancers may have increased with the development and industrialization of modern society (2012) [11]. Currently cancer mortality is second only to cardiovascular mortality [11,16]. Indeed, a terracotta torso which was excavated in Anatolia (todays Turkey) dates from 200 to 100 BC, and resides in the collections of the Institute for Medical History in Jena, Germany, illustrates one of earliest accountable depiction of cancerous female breast in art, while the celebrated Renaissance sculpture “Notte” by Michelangelo is considered to be the first known portrayal of advanced breast cancer in modern history [17]. Similarly, the belief that cancers could be transmissible goes back as early as 16th century [17].

Currently, approximately a quarter of the worldwide malignancies are attributed to microbial contribution [18] and orodigestive cancers are among the top five leading causes of cancer mortalities [16]. One of the particularly devastating examples of orodigestive cancer mortality with escalating prevalence is oral squamous cell carcinoma (OSCC), which claims an estimated 7500 lives yearly in the United States [19]. Importantly, the increasing incidence of OSCC does not seem to correlate with the presence of commonly accepted risk factors, such as tobacco and alcohol consumption [20]. Further, Human Papilloma Virus, that has been attributed as major etiological agent for oropharyngeal cancers of the head and neck is only present in 2–4% of OSCCs [20]. Accordingly, there are no reliable diagnostic markers and/or risk factors present for early identification of OSCC cases along with the other cancers of the orodigestive tract, encompassing the oral cavity, upper intestinal tract, and pancreas. A number of recent epidemiological/clinical studies, including case–control and cohort studies, described strong associations of periodontal disease and/or tooth loss with cancers of the orodigestive system, and suggested the involvement of select oral microbes in the development of orodigestive malignancies [19]. Accordingly, a successful oral colonizer and well recognized periodontal pathogen, *P. gingivalis* was identified among the known microbial species of the oral cavity to have the highest correlation with OSCC [19,21], followed by associations with pancreatic cancer, where *P. gingivalis* was found to be an important independent risk factor [19,22,23]. *F. nucleatum*, another well-known opportunistic microorganism which has been long considered as a commensal bacterium in the oral cavity, only recently was elevated to a pathogenic agent status [24] having a propensity for colonization also of the lower gastrointestinal tract, and proposed to take part in inflammatory bowel disease and exclusively in colorectal cancer [8,12,22,24,25].

Although specific data about the role of other species of the oral ecosystems are very sparse, the oral microbial profiles as “danger signatures” with potential to drive the host to a dysbiotic state are newly postulated for some other chronic disease progressions. Along the same lines, a recent clinical cohort study, showed the shifts in the abundance of operational taxonomic units (OTUs) in OSCC cancer and pre-cancer patients, when compared to healthy subjects [20]. The study described increased amounts of phylum *Bacteroidetes*, and specifically genera *Porphyromonas* and *Prevotella*, and decreased *Firmicutes* and *Actinobacterium* phyla, and particularly *Streptotococcus* and *Rothia* species in swabs of cancer subjects compared to clinically normal patients using 16S qPCR detection and metagenomics analysis [20]. More critically, in the same study a significant increase of *P. gingivalis* was detected in both pre-malignant and malignant samples of patients, when compared to healthy controls. Whereas *Prevotella* species were increased only in oral cancer patients, but not in pre-malignant patients, suggesting a potentially secondary colonization of cancer tissues by *Prevotella* species,