Oral Science International xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Oral Science International

journal homepage: www.elsevier.com/locate/osi

Review

Human diseases, immunity and the oral microbiota—Insights gained from metagenomic studies

Adi Idris[a,*], Sumaira Z. Hasnain[b], Lu Z. Huat[a], David Koh[a,c]

[a] PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Brunei Darussalam
[b] Translational Research Institute, University of Queensland, Brisbane, Queensland, Australia
[c] Saw Swee Hock School of Public Health, National University of Singapore, Singapore

ARTICLE INFO

Article history:
Received 21 September 2016
Received in revised form 8 November 2016
Accepted 14 December 2016
Available online xxx

Keywords:
16S rRNA
Immune system
Metagenomics
Oral microbiota
Saliva

ABSTRACT

The immune system consists of a complex but organised myriad of cell types that continually maintain and survey their resident environment. It is this balanced homeostatic relationship between the cells of the immune system and its surrounding environment that shapes the microbial flora. In the oral cavity, the immune system not only has to harmonise with the ecology of commensal bacteria, fungi and viruses but also should be able to defend against pathogenic microbes. In fact, the oral microbiota is altered in situations when the immune system is dysregulated. There are a number of human diseases or conditions that perturb the balance of the host immune system and have an effect on the host oral microbiota. If this balance is disturbed, the symbiotic relationship will shift to allow the colonisation or overgrowth of potentially pathogenic species, inducing a pathogenic process that leads to various disease symptoms. The dynamics balance between the immune status and the oral microbial community of an individual has remained understudied till recently. Advances in metagenomics allow detailed investigations into oral microbial population and the possible diversity. This concise review summarises the current findings using metagenomic approaches for studying oral microbial flora diversity.

Contents

1. Introduction

The human microbiota is a dynamic ecological community that consists of multiple taxa, each potentially interacting with each other, the host and the environment [1]. They colonise the epithelial surfaces of barrier sites that separate the contaminated external environment and the sterile host interior environment, including the skin, gut and the oral cavity. It is clear that the commensal microbial flora can shape the local immune system in some of these sites as a way to maintain a 'healthy homeostasis' between the host and the microbe. The coevolution of these resident commensals allows the establishment of an appropriate level of immune activation required for the immune fitness of the host.

* Corresponding author at: PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Jalan Tungku Link Gadong, BE1410, Brunei Darussalam.
E-mail address: adi.diris@gmail.com (A. Idris).

http://dx.doi.org/10.1016/S1348-8643(16)30024-6
1348-8643/

Both the host immune system and resident commensal flora can influence one another to maintain homeostasis. A dysbiosis in the microbiota will inevitably lead to a dysregulation of the local immune response at that site. In the gut, commensal bacteria can modulate the differentiation of different T cell subsets, such as T-helper 17 [2] and immunoglobulin A (IgA)-secreting cells [3]. Commensal skin bacteria can also modulate local skin immunity where bacterial products released by resident skin staphylococci can modulate protective innate immune responses against skin injury [4]. *Staphylococcus aureus* is found in high amounts on the skin of patients with atopic dermatitis, an inflammatory condition of the skin [5], suggesting that commensal skin flora can drive local inflammatory processes. Similarly, alterations in the immune status of the human host would affect the diversity of the local microbiota, which results in pathology. Several animal models of inflammation have been used to show the aberrant effect of a dysfunctional immune system on the microbiotas of the gut [6,7] and the skin [8]. Hitherto, research has focussed mainly on the host immune system's interplay with the gut microbiota. With advances in next-generation sequencing (NGS) techniques, research into the oral microbiota is gaining interest among researchers across different disciplines.

The aim of this review is to highlight the importance of the host immune system in shaping the oral microbiota, with a strong focus on how NGS techniques are changing the face of the oral microbiota field. Given that the majority of the current research on oral microbiotas is on the domain bacteria, this review mostly focusses on discussing the current developments in dissecting the interplay between the host immune system and oral bacteria.

2. The human oral microbiota

The oral cavity acts as a major gateway into the human body. The oral cavity is a complex microenvironment consisting of prokaryotic (i.e. bacteria and viruses) and eukaryotic (i.e. fungi) microbes that coexist within the host environment. However, it is important that the host environment has both the ability to limit microbial burden and limit the host damage caused by an uncontrolled response. However, the oral cavity is subjected to a plethora of physical and micro-environmental insults, which include pH changes in the oral cavity, changes in the diet of the host, and the external environment (e.g. climate and air pollution). All these factors together account for the vast phenotypic and genetic variation in the oral microbial community between different individuals. Taking into account all the above-mentioned factors, the immune system, which determines the health status of the host, plays a crucial role in shaping the oral microbiota. In the human host, the role of the immune status in shaping the composition of oral microbiota is largely unknown.

The oral cavity harbours a complex community of microbes including viruses, fungi, protozoa, archaea and bacteria. However, bacteria are the most common microbial agents for causing oral diseases in human. With over 1000 species of bacteria being commensal residents in the oral cavity, the oral cavity is by far contains the second most complex microflora in the body after the gut [9]. One of the limitations of using traditional culture-dependent methods for determining the true extent of the complexity of the oral microbial composition warranted the use of high-throughput NGS methods to 'fill in the gaps'. Less than 50% of the bacterial species present in the oral cavity can be cultivated using anaerobic microbiological methods [10]. NGS technology overcomes this problem by identifying these previously 'unculturable' bacteria.

The bacterial community of the mouth consist mostly of the Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Spirochaetes and Fusobacteria phyla, and the key features of these predominant bacterial taxa have been previously described [9]. The bacterial genera and phyla list is continually updated in the publicly available Human Oral Microbiota (HOM) database (Table 1) [11]. The HOM project revealed that each individual has a unique microbiota. The 'true' composition of the oral microbiota is not easy to determine as the oral cavity is continuously exposed to the external environment, which allows exogenous microbes, air and food to enter the oral space. This makes the oral microbiota the most dynamic microbiotas in the human body where commensal population is amenable to change.

Table 1
The major bacterial phyla and classes present in the human oral cavity [11].

Phylum	Class
Actinobacteria	Actinobacteria
Bacteroidetes	Bacteroidetes [C-1] Bacteroidetes [C-2] Bacteroidia Flavobacteriia Sphingobacteriia
Chlamydiae	Chlamydiia
Chlorobi	Chlorobia Ignavibacteria
Chloroflexi	Anaerolineae Caldilineae
Firmicutes	Bacilli Clostridia Erysipelotrichia Mollicutes Negativicutes
Fusobacteria	Fusobacteriia
Gracilibacteria (GN02)	GN02 [C-1] GN02 [C-2]
Proteobacteria	Alphaproteobacteria Betaproteobacteria Deltaproteobacteria Epsilonproteobacteria Gammaproteobacteria
Saccharibacteria (TM7)	TM7 [C-1]
Spirochaetes	Spirochaetia
SR1	SR1 [C-1] SR1 [C-2] SR1 [C-3]
Synergistetes	Synergistia
WPS-2	WPS-2 [C-1]

3. Unravelling the oral microbiota—the metagenomic approach

Traditional bacteriological culture-based techniques are limited only to cultivatable oral microbes, therefore underestimating the 'true' biodiversity of the oral microbiota. Furthermore, there are practical problems in culturing anaerobic bacteria from the oral cavity. With advances in 16S ribosomal RNA (rRNA) and high-throughput sequencing technology, we can now detect both uncultivatable and cultivatable microbes in the oral cavity. There is an emerging body of literature that uses NGS technology to characterise the oral microbiota in immunocompromised conditions such as auto-immune disorders and cancers (discussed below).

To date, the use of high-throughput sequencing of 16S rRNA is the method of choice for researchers in the oral microbiota field including the HOM project [11]. Despite 16S rRNA sequencing offering the advantage of generating a high number of sequences (although shorter in length), caution has to be taken when

Please cite this article in press as: Idris A, et al. **Human diseases, immunity and the oral microbiota—Insights gained from metagenomic studies**. Oral Sci Int (2017), http://dx.doi.org/10.1016/S1348-8643(16)30024-6