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Review

Composition of gut microbiota and its influence on the immunogenicity of oral rotavirus vaccines

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ABSTRACT

The introduction of oral rotavirus vaccines (ORVVs) has led to a reduction in number of hospitalisations and deaths due to rotavirus (RV) infection. However, the efficacy of the vaccines has been varied with low-income countries showing significantly lower efficacy as compared to high-income countries. The reasons for the disparity are not fully understood but are thought to be multi-factorial. In this review article, we discuss the concept that the disparity in the efficacy of oral rotavirus vaccines between the higher and lower socio-economical countries could be due the nature of the bacteria that colonises and establishes in the gut early in life. We further discuss recent studies that has demonstrated significant correlations between the composition of the gut bacteria and the immunogenicity of oral vaccines, and their implications in the development of novel oral RV vaccines or redesigning the current ones for maximum impact.

Contents

1. Introduction

Rotaviruses (RV) are the leading cause of diarrhoeal disease in young children worldwide. The infection is mostly mild but can be severe, leading to hospitalisation and death especially in low income settings. An estimated 450,000 RV deaths occur annually in children under the age of five and over 90% of these occur in sub-Saharan Africa and South-East Asian countries [1]. The introduction of the oral RV vaccines (ORVVs) has seen the drop in number of hospitalisations and deaths globally [2,3]. However, the efficacy of the vaccines have been varied, with low income countries showing significantly lower efficacy [4–6] as compared to efficacy of over 90% in higher income countries in America and Europe [7–10]. Reasons for the disparity in vaccine efficacy between the two-income resource settings are not fully understood but are thought to be multi-factorial [11]. They include the inhibitory

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effect of titres of maternal antibodies acquired through placenta or breast milk i.e. breast milk-derived RV-specific IgA [12,13], interference from co-administered oral vaccines such as polio vaccine [14], HLA blood group antigen type [15]. Poor nutrition, environmental entropy, chronic and co-infections that may suppress immune response to the RV vaccination has also been suggested (not known if infants can develop micronutrition deficiencies, environmental entropy and coinfections as older children) [reviewed in 11]. Recent evidence (discussed later) suggests that the composition and diversity of the gut microbiota, especially bacteria, could have an impact on the immunogenicity of the oral RV and other oral vaccines.

The human gastrointestinal tract harbours a variety of commensal bacteria that co-evolved with the host in a symbiotic relationship in which the host provide the microbiota with a nurturing niche for growth and survival, while the commensal bacteria influence many physiological processes beneficial to the host [16]. Some of these processes include nutrient acquisition, energy metabolism and outcompeting invading exogenous and pathogenic bacteria by occupying the luminal niches [16–18]. Another beneficial effect of the gut microbiota that has recently been recognised is the aiding of the development, maturation and function of the mucosal immune system [19]. This is best demonstrated in germ-free mice, which possesses an underdeveloped immune system. Introduction of commensal bacteria restores the characteristics of a mature immune system [20–22]. As the commensal bacteria affects the development, maturation and function of the mucosal immune system, it is logical to consider it can also affect the host's response to oral vaccines. Indeed colonisation of gnotobiotic mice by segmented filamentous bacteria (non-culturable *Clostridium*-related species) has been shown to induce intestinal T cell adaptive functions [23]. In this review, we summarise the events that occur during early bacterial colonisation of the gut and how its outcome can profoundly affects the wellbeing of the individual, including the development and maturation of mucosal immunity. We further discuss the concept that the disparity in the efficacy of oral RV vaccines between the rich and poor countries could be due the nature of the bacteria that colonises and establishes in the gut early in life. Understanding the reasons for the underperformance of the ORVs in poor countries is important so that the right interventions are designed to maximise the impact of the current vaccines or guide the development of new ones.

2. Early colonisation shapes the composition of gut microbiota and future immune response of the host

The composition of the gut microbiota in adults is shaped early during the first three years of life. During this period, the composition of gut microbiota is said to be highly variable and unstable [24,25]. Due to its positive oxidation/reduction potential at birth, the sterile intestinal tract of the infant is first colonised by facultative anaerobes such as lactobacilli, enterobacteria and enterococci. As the environment in the gut changes to a more reduced one due to depletion of oxygen by the first colonisers, strict anaerobes such *Bacteroides* (phylum Bacteroidetes), *Bifidobacterium* (phylum Actinobacteria), *Clostridium* species (phylum Firmicutes) subsequently flourishes [26,27]. The composition of bacteria colonising the gut of the infants during early days of life is influenced by several factors including the method of child's birth delivery (vaginal vs caesarean section), infant feeding habits (breast-fed vs formula fed) and sanitation (hygienic vs unhygienic) [24,28]. Formula-fed infants have significantly lower counts of probiotic bacteria such as *Bifidobacteria*, *Lactobacillus* and *Streptococcus* than breast-fed children do. Conversely, these infants have elevated levels of *Clostridium difficile*, *Escherichia coli* and *Klebsiella* species as compared to their breast-fed counterparts [29–31]. Infants born naturally through the vagina are likely to be colonised early by vaginal or faecal bacteria from their mothers whereas caesarean-section born infants are likely to be colonised by bacteria from the skin of health care workers and the hospital environment [26,32]. The composition of gut microbiota of infants exposed to different sanitary conditions are said to be different, with those exposed to rampant poor sanitation reported be distinct, more diverse and variable than that of their counterparts from good sanitation background [33,34]. Other important determinants of bacterial composition of the infants' gut are gestation age, infant hospitalisation and antibiotic treatment [24].

By the age of two, the mixture of gut bacteria in infants become generally similar to those found in adults [25] and by three, its composition and diversity fully resembles that of adults [35,36] and remains relatively stable over time. Analysis of the human gut microbiota using the small subunit 16S ribosomal RNA gene sequences reveals that Firmicutes and Bacteroides are the dominant phyla [37]. At phylum level, the composition of gut bacteria is similar among individuals but varies at species and strain level [38]. The type of bacteria that colonises and establishes in the luminal niches of the gastrointestinal track of infants can have profound effects early and later in life [39]. Early colonisation of the gut by appropriate proportions of commensal bacteria promotes the health of the infant through several mechanisms, including appropriate development and maturity of the mucosal immunity [40,19] that may later enhance response to oral vaccines. There are reports that suggest the existence of a window period immediately after birth in which the consortium of bacteria acquired plays a crucial role in directing future host immune response profile. For example, germ-free mice colonised with caecal contents at week three postnatal had an increased proinflammatory immune responses than those colonised during the first week or later [22]. In human studies, infants colonised by certain members of gut microbiota during the first 8 weeks of life had significantly higher counts of $CD27^+$ memory B cells than those colonised at other periods [41]. These immunomodulatory effects are not confined to mucosal immunity only but to the systemic immunity as well [42].

3. Composition of gut microbiota affects the development and function of the host immune system

Comparative studies have shown that germ-free mice possess underdeveloped mucosal immune tissue characteristics. However, these characteristics, which include induction of secretory IgA (sIgA), increase in $CD4^+$ T cell numbers as well as a well-developed and organised gut-associated lymphoid tissue (GALT), are restored when commensal bacteria are introduced in the gut [20–22]. Recent studies have revealed the existence of several members of the gut microbiota possessing specific immunomodulatory capabilities that differentially regulate the development of various immune cell groups [42] (Table 1). This suggests that variations in the composition and diversity of the gut bacteria may contribute to individual differences in immune response to infection or oral live attenuated vaccines. For example, *Bacteroides fragilis*, a Gram-negative bacteria belonging to phylum Bacteroidetes, affect mucosal T cell homeostasis by promoting not only Th1 systematic development [43] but also regulatory T cell function [44]. A bacterial polysaccharide (PSA) produced by *B. flagilis* during early colonisation of the gut has been shown to promote the cellular and physical maturation of the developing immune system [43]. Colonisation of the gut of germ-free animals with PSA producing *B. flagilis* restored the systemic T cell insufficiencies and Th1/Th2

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