Influence of the Host Factors on Human Papillomavirus Infection and Vaccine Efficacy

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Human papillomavirus (HPV) is associated with cervical cell changes, genital warts, recurrent respiratory papillomatosis, laryngeal papillomatosis, head and neck cancer, and cervical cancer. Two commercial HPV vaccines have successfully been made available in the clinical field. This review covers the progress of cervical disease by understanding the nature of HPV infection, as well as the relationship between the host factors and HPV vaccine effectiveness. Among these host factors, microbiota has been revealed to influence the development and function of both the innate and adaptive immune systems. Therefore, the composition of the microbiome may ultimately affect vaccine effectiveness. Understanding the relationship between host factors and HPV infection/vaccine efficacy may prove to be useful in earlier diagnosis, as well as disease prophylaxis.

Key Words: HPV, Vaccine efficacy, Probiotics, Microbiota

INTRODUCTION

Humans are constantly exposed to pathogenic microorganisms, including viruses, bacteria, and fungi. Among these microorganisms, human papillomavirus (HPV) is the most common sexually transmitted infection worldwide (1). Currently, two HPV commercial vaccines have been approved for use in the clinical field. These are termed 'Gardasil' and 'Cervarix', which cover 4 (6, 11, 16 and 18) and 2 (16 and 18) HPV types, respectively (2). In December 2014, Gardasil 9 was approved in the USA, which covers 9 HPV types (6, 11, 16, 18, 31, 33, 45, 52, and 58) (3). The characters of these HPV vaccines are summarized in Table 1. While the mechanism of HPV infection and the subsequent development of cervical cancers have been extensively studied, there are many unknowns in the relationship between the host factors (e.g. genetic polymorphism, microbiome, disease status, and immune system) and HPV vaccine effectiveness. Among the various host factors affecting vaccine efficacy, the role of the microbiome has now been established (4, 5). In this review, we will summarize the recent data on the relationship between the host factors, especially microbiota composition, and both HPV vaccine efficacy and HPV infection.

Basics of HPV infection

HPV is a circular double-stranded DNA (dsDNA) virus for which more than 200 different types have been identified
and categorized into high- and low risk (6). HPV has a non-enveloped, icosahedral capsid, and infects only mucosal or cutaneous epithelium (7). The fifteen types of HPV classified as high risk include HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 (8). In particular, HPV 16 and 18 are known to cause up to 70% of cervical cancers (9). The low risk HPV types include types 6, 11, 42, 43, and 44, which are involved in the development of cervical cell changes, genital warts, recurrent respiratory papillomatosis, and laryngeal papillomatosis (10–12).

Cervical cancer, the second most prevalent cancer among women, is associated with HPV infection (13). To detect potentially dangerous HPV strains and to defend against infection, humans have developed effective innate and adaptive immune systems that minimize the impact of pathogens on human health. On the other hand, HPV uses specific life strategies to enable its survival and persistence within the epithelial cells, including diverse mechanisms to evade host immune surveillance via programming for natural cell death, which causes the progeny virions only to be released in high quantities from terminally differentiated epithelial cells (14). HPV infects only mucosal or cutaneous epithelium. In addition, HPV induces a slow and weak immune response, which inhibits interferon synthesis (15, 16).

The HPV genome encodes two structural capsid proteins (L1 and L2) and three oncoproteins (E5, E6 and E7) (17, 18). The major capsid protein L1 self-assembles into virus-like particles (VLPs), which are in tertiary or native form and are assembled as multimers to generate neutralizing antibodies. HPV L1 VLP vaccines have been developed commercially (Table 1). VLP vaccines are highly immunogenic and induce HPV neutralizing antibodies, which persist for at least 5 years after immunization. The HPV E5 protein suppresses the expression of MHC class I and antigen processing via the transporter associated with the antigen processing pathway (19, 20). HPV E6 ubiquitinates (ubiquitin mediated degradation) the p53 tumor suppressor protein (21), whereas E7 ubiquitinates the retinoblastoma (pRb) tumor suppressor protein (22), indicating that these two proteins may have oncogenic effects. In addition, the HPV E6 protein blocks cell cycle regulatory genes required for G1/S transition and DNA replication. These proteins (E5, E6 and E7) are also able to break antigen presentation (25) (Fig. 1). Therefore, these three proteins also play roles in the evasion of the innate and adaptive immune system, which creates a favorable

Table 1. Characteristics of anti-HPV vaccines

<table>
<thead>
<tr>
<th>Commercial name</th>
<th>Bivalent vaccine</th>
<th>Quadrivalent vaccine</th>
<th>Ninevalent vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP types</td>
<td>HPV 16/18</td>
<td>HPV 6/11/16/18</td>
<td>HPV 6/11/16/18/31/33/45/52/58</td>
</tr>
<tr>
<td>Producer cells</td>
<td><em>Trichoplusia</em> ni (Hi 5) insect cell line infected with L1 recombinant baculovirus</td>
<td><em>Saccharomyces cerevisiae</em> expressing L1</td>
<td><em>Saccharomyces cerevisiae</em> expressing L1</td>
</tr>
<tr>
<td>Administration schedule</td>
<td>Girls and women: 9~14 years: 0, 1, 6 months</td>
<td>Girls and women: 9~13 years: 0, 2, 6 months</td>
<td>Girls and women: 9<del>26 years: 0, 2, 6 months Boys: 9</del>15 years: 0, 2, 6 months</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>Aluminum hydroxyphosphate sulfate</td>
<td>Aluminum hydroxide and 3-O-deacylated-4-monophosphoryl lipid A</td>
<td>Aluminum hydroxyphosphate sulfate or AAHS</td>
</tr>
</tbody>
</table>
Host Factor Ramifications on Vaccination

Environment for viral replication (26). It is thought that E6 and E7, from the low risk HPV types, may have weaker binding to their target proteins compared to the high risk types (27).

Factors affecting HPV infection and vaccine

Many factors affect HPV infection, including sex, estrogen hormones, microbiome, genetics, epigenetic phenomena, age, nutrition, immune system, and infectious and autoimmune diseases (28, 29).

1. Impact of host genetic factors on HPV infection

Population based association studies (genetic polymorphisms) often estimate the risk of developing a certain disease in carriers and noncarriers of a particular genetic polymorphism (30). The population genetic background contributes to the susceptibility to developing cervical cancer after HPV infection. The p53 Pro/p53 Arg polymorphism should influence the outcome of HPV infection, because the presence of heterozygous p53 Pro is more resistant than p53 Arg to E6-mediated degradation. Those with the p53 Arg allele, in the absence of the p53 Pro allele, are therefore at increased risk of developing cervical cancer (31).
Moreover, polymorphism in the proinflammatory cytokine gene Tumor necrosis factor-α (TNF-α) also causes increased risk of HPV associated cervical cancer in the presence of HPV. TNF-α-308 G/A polymorphism may play a role in TNF-α production and the inflammatory response during the course of cervical cancer. In particular, the A allele is associated with an increased risk of invasive cervical cancer (32, 33). Individuals with the TNF-α-308 G/A and -238 G/A promoter genotypes are at increased risk of developing inflammatory, infectious and autoimmune disease (33). These results suggest that host genetic polymorphisms can influence the nature and extent of HPV-mediated disease.

2. Impact of host microbiome on metabolic disorder and chronic inflammatory disease

The interplay between HPV, the gut epithelium, and host innate defense responses is among the most critical factors determining the fate of HPV infections and disease outcomes. Recently, gut microbiota were found to contribute to many host physiological processes and disease (34, 35). Theses intestinal microbiota make important contributions to the health of their hosts by protect against pathogens via appropriate development of the immune system and synthesis of essential vitamins (35, 36). It should also be noted that these essential vitamins, such as vitamin A and D, are also important for immune function and vaccine effectiveness (37). In addition, there is an abundance of NK, Th17 and Treg cells in the intestinal mucosa, and their accumulation and function are affected by the presence of the microbiota (38). Infant gut microbiota has a relatively simple composition, which is affected in large part by the maternal microbiota due to the delivery method, such as cesarean or vaginal birth (39). Moreover, community and function of the microbiota can change owing to numerous variables, including lifestyle, diet, hygiene, and use of antibiotics (40).

Two of the main types of intestinal microbes, the Firmicutes and Bacteroidetes, have also been linked to obesity and metabolic disorders (41–43). Furthermore, microbiota composition is also related to incidence of chronic inflammatory diseases, such as allergic conditions, chronic colitis, and autoimmune disorders (44–51).

3. Impact of host immune factor on intestinal microbiota

Recognition of microorganisms by the innate immune system involves pattern recognition receptors (PRRs), such as nucleotide binding oligomerization domain (Nod) like receptors (NLRs) and Toll like receptors (TLRs), which discriminate pathogen associated molecular patterns (PAMPs) or danger associated molecular patterns (DAMPs) (52–54). Extracellular contaminants are recognized by TLRs, whereas surveillance of the cytoplasm is the work of NLRs, recognized by their Nods (52, 55). Among the various TLRs, TLR4 recognizes pathogen bacterial LPS, but is not stimulated by commensal microflora, which have detoxified forms of LPS, dephosphorylated by an intestine-specific isoform of alkaline phosphatase (36). TLR5 recognizes bacterial flagella, and its signaling can stimulate CD11chighCD11ehigh DCs to express Raldh2, which catalyzes the conversion of vitamin A to retinoic acid. Retinoic acid can then cause B cells to differentiate into IgA producing plasma cells (56). Secreted IgA is required for keeping commensal bacteria that can determine the nature of bacteria. IgA regulates the ecological balance of microbiota, which regulates the composition and character of microbiota. IgA protects against viruses from the epithelium by binding, rather than cellular neutralization. Furthermore, IgA, an adaptive response effector, is crucial for the compartmentalization of the microbiota to the intestinal lumen (57) (Fig. 2). However, Tlr5–/– mice exhibit similar changes in the microbiota shape as ob/ob mice (leptin gene deficiency). The Tlr5–/– phenotype is due to changes in the microbiota, causing hyperphagia and metabolic syndromes, including insulin resistance, hyperlipidemia, and obesity (43). TLR9 recognizes the viral or bacterial dsDNA derived CpG motifs, but its transcription is inhibited by recombinant HPV 16 E6 and E7 (26).

TLR2 and Nod2 are both required for the transcriptional induction of pro IL-1β and the priming of the inflammasome, which is mediated by the upregulation of NLRP3 (58). Inflammasome activation is thought to require two signals, the first involving the sensing of conserved PAMPs which induce expression of certain inflammasome components and
Host Factor Ramifications on Vaccination

Cytokines, and the second involving disruption of cellular membranes or signaling pathways (59). Cytosolic dsDNA from intracellular pathogens such as HPV is sensed by AIM2, which triggers formation of the inflammasome complex with ASC to activate caspase 1-mediated processing of IL-1β and IL-18 (60, 61). Recent studies have suggested that inflammasome deficiency may be associated with stimulator-induced inflammation, inducing tumorigenesis in the intestine and chemical colitis, due to alterations in the microbiota and the emergence of normally suppressed bacteria that have proinflammatory activities (46, 62, 63). Nod2−/− mice are susceptible to pathogen infection because of an intrinsic defect in their ability to kill the bacteria. In addition, these mice also have increased populations of commensal bacteria in the intestine, suggesting that NOD2 plays a crucial role in regulating homeostasis between bacterial flora and innate immunity (64). Moreover, NLRP6 deficient mice exhibited increased members of Prevotellaceae and TM7, and reduced members of Lactobacillus, which caused increased intestinal inflammatory cell recruit-

Figure 2. A schematic diagram of possible mode for the relationship between the microbiota and the immune system in the intestinal lamina propria. The microbiota is composed of a variety of bacteria with different characters. The microbiota influence the development and function of both the innate and adaptive immune systems. The intestinal microflora has TLR5 ligands such as flagellin. TLR5 signaling stimulates CD11c hiCD11b hi DCs, which can catalyze the conversion of vitamin A to retinoic acid; this causes B cells to differentiate into IgA producing plasma cells. Secreted IgA regulates the ecological balance of microbiota, which regulates the composition and character of microbiota. Ultimately, IgA induces compartmentalization of the microbiota to the intestinal lumen, and it contributes to protection from viral infections. HPV, human papillomavirus; TLR5, toll like receptor 5; DC, dendritic cell; IgA, immunoglobulin A; Raldh2, retinaldehyde dehydrogenase 2.
ment and susceptibility to chemically induced colitis. These mice phenotypes resembled ASC−/− mice (46). Therefore, host immune factors may drive disease-specific alterations in the microbiota, which in turn may promote the development of disease in the host.

4. Impact of host microbiome on HPV vaccine efficacy

The human intestinal tract harbors a large number of species which intimately interact with nutrition status, genetics, metabolism, and the immune system (65). The microbiota ultimately contribute to host physiology via fostering normal development of the immune system and influencing the ensuing immune responses. Interestingly, vaccines often have lower effectiveness than expected when used in developing countries, possibly due to intestinal dysbiosis, malnutrition, or hygiene (66), which may easily affect the microbiota composition. Consequently, based on these well-founded conjectures, microbiota may affect vaccine responses indirectly or directly through action on various immune responses, such as development of CD4+ T cells (67). Immunization is necessary to prevent morbidity and mortality from infectious diseases, such as HPV. Actually, the main goal of vaccination is to elicit memory B cell responses and CD4+ T cell-mediated neutralizing immune effector responses. B cell memory response to antigen recall is an important factor for the long-term efficacy of vaccine-induced humoral protection. The protection achieved by HPV vaccines against incident HPV infection and HPV-associated pathology is mediated via serum neutralizing IgG (68). By the way, recent studies have shown a trend

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<thead>
<tr>
<th>Probiotics</th>
<th>Vaccines</th>
<th>Biological effects</th>
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<tbody>
<tr>
<td><em>Lactobacillus casei</em> strain GG (LGG)</td>
<td>D x RRV rhesus-human reassortant rotavirus vaccine</td>
<td>LGG has an immunostimulating effect on rotavirus vaccination via enhance IgA production and release of interferon γ.</td>
</tr>
<tr>
<td>LGG or <em>Lactococcus lactis</em> (L. lactis)</td>
<td><em>Salmonella typhi</em> Ty21a vaccine</td>
<td>LGG stimulated IgA sASC responses against S. typhi Ty21a. <em>L. lactis</em> has increase CR3 receptor expression on the neutrophils which can influence the non-specific immune response.</td>
</tr>
<tr>
<td>LGG and <em>Bifidobacterium lactis</em> BB12 (BB12)</td>
<td>AttHRV vaccine</td>
<td>LGG and BB12 acted as an immunostimulant for AttHRV vaccine via modulated DC activation and responses.</td>
</tr>
<tr>
<td><em>L. lactis</em>, <em>Lactobacillus plantarum</em> or <em>Bifidobacterium bifidum</em></td>
<td>Allergy vaccines</td>
<td>These bacteria have induction of Th1 response in eczema and asthma models.</td>
</tr>
<tr>
<td><em>Mycobacterium vaccae</em> (M. vaccae)</td>
<td>Allergy vaccines</td>
<td>Heat-killed M. vaccae induces Treg cells and decreases airway inflammation in atopic dermatitis or asthma murine model.</td>
</tr>
<tr>
<td><em>Bifidobacterium breve</em> strain Yakult (BBG-01)</td>
<td>Cholera vaccine</td>
<td>A trend towards increased serum IgG after administration of BBG-01</td>
</tr>
<tr>
<td><em>Bifidobacterium longum</em> BL999 (BL999) and <em>Lactobacillus rhamnosus</em> LPR (LPR)</td>
<td>Hepatitis B vaccine</td>
<td>BL999 and LPR were improved HepB surface antibody responses in subjects.</td>
</tr>
<tr>
<td><em>Lactobacillus paracasei</em> ssp. F19 (LF19)</td>
<td>Diphtheria, tetanus and Hib vaccines</td>
<td>LF19 was increased the capacity to raise immune responses in infants breastfed &lt; 6 months.</td>
</tr>
<tr>
<td>LGG</td>
<td>Live attenuated influenza vaccines</td>
<td>LGG was increased protective hemagglutinin inhibition titers.</td>
</tr>
<tr>
<td><em>L. fermentum</em> CECT5716 (LLECT5716)</td>
<td>Inactivated influenza vaccine</td>
<td>A trend towards increased TNF-α, total IgG and IgM, and influenza-specific IgA after administration of LECT5716.</td>
</tr>
<tr>
<td>BB12 and L. paracasei 431 (L431)</td>
<td>Inactivated influenza vaccine</td>
<td>BB12 and L431 were elevated influenza specific IgG levels and influenza specific IgA responses.</td>
</tr>
</tbody>
</table>
towards increased serum IgG after administration of probiotics (69, 70). However, probiotic formulations may not improve the response to a particular vaccine (71). The recent data regarding the relationship between probiotic treatment and vaccine efficacy are summarized in Table 2. Taken together, these data indicate that the effects of probiotics on vaccine efficacy may be dependent on the types of vaccines (69, 70, 72~77). However, the detailed mechanisms urgently need to be revealed.

Meanwhile, healthy vaginal microbiota is composed primarily of lactic acid producing bacteria, which contribute to women's health by maintaining a low pH in the vagina (5). Abnormal vaginal microbiota might act as a cofactor for the acquisition of HPV. Especially, L. gasseri and Gardnerella vaginalis were detected more frequently, along with a significantly higher diversity of the microbiota in HPV-infected women than in HPV negative women (78). Ultimately, the composition of the vaginal microbiota may affect HPV infection and disease progression.

CONCLUDING REMARKS

As mentioned above, HPV infection may be at least partially dependent on vaginal microbiota composition, whereas the efficacy of the HPV vaccine may be dependent on the intestinal microbiota composition. However, to the best of our knowledge, direct evidence for the relationship between HPV vaccine efficacy and microbiota composition has not yet been provided. Therefore, research of the interaction between the host factors, especially microbiota, and HPV vaccine effectiveness is needed to enhance our understanding of the HPV-related disease, cervical cancer, and to guarantee its prevention.

Footnotes

Disclosure: The authors have no conflicts of interest and nothing to disclose.

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