Alterations of Vaginal Microbiota and Chlamydiatrachomatis

Subjects: Infectious Diseases
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Alterations of Vaginal Microbiota and *Chlamydia trachomatis* as crucial co-causative factors in cervical cancer genesis procured by HPV. Nowadays, it is widely accepted that some types of infections caused by certain viruses, bacteria, and parasites may be the cause of high-risk factors for several types of cancer in humans. These pathogens evolved strategies to hamper the host's integrity of defense such as the prevention of the apoptosis mechanism pathway of the damaged cells reducing the ability to repair the damage(s) and eventually resulting in cellular transformation, cancer progression, and reduced response to therapy.

Keywords: reactive species of the oxygen (ROS) ; human papilloma virus (HPV) ; Chlamydia trachomatis ; vaginal microbiota ; sexual transmitted infections (STIs) ; Cervix Cancer (CC)

1. Introduction

Chlamydia trachomatis and human papillomavirus (HPV) are the most common pathogens belonging to sexually transmitted infections (STIs), and both are known to increase the risk of cervical cancer (CC) and infertility. Nevertheless, the current point of view is that both pathogens are considered just co-factors for CC development, whilst the whole process should be related to multiple conditions. The main issue is practically linked to the individual's immune condition, age, genetic make-up, and microbiota homogeneity and stability as most HPV and *C trachomatis* infections related to the female genital tract are facilitated by the decay of the first line of defense in the vaginal environment, constituted by a healthy vaginal microbiome characterized by a net equilibrium of all its components. Thus, the aim of this paper was to highlight the complexity and fragility of the vaginal microenvironment. Accentuating the fundamental role of all elements and systems involved including different Lactobacillus strains and the immune-endocrine system in preserving it from oncogenic mutation.

2. The Immune Profile of CC Microenvironment *C trachomatis* and HPV Crosstalk

The risk of CC is a multifactorial matter, involving different factors and variants. The HPV-*C trachomatis* DNA host integration is usually a necessary event in the pathogenesis of HPV-*C trachomatis* related cancer; however, the mechanism of reciprocal validation and integration needs probably years and takes place in specific microenvironment conditions. In addition, one has to consider that any breaks or damage in the local immune surveillance must be also facilitated by either genetics or epigenetics factors for the integration occurs. In this regard, studies have shown that viral-bacteria integration is indeed eased by local dysbiosis which in turn increases pathogens' indiscriminate invasion and persistent inflammatory state. Furthermore, aging, (hormones unbalances) and diet also showed have detrimental effects contributing to inflammation raise and ROS uncontrolled persistence. Together these heterogeneous factors lead to host cells' DNA strand breaks enabling a stronger HPV - *C trachomatis* reciprocal integration. Consistent with this assumption, the silent long-term HPV - *C trachomatis* co-infections become the essential contributors to tissue transformation which drives to final CC. The prevalence of co-infection of *C trachomatis* and HPV is therefore an important contributory fact that may begin at a young age and silently persist as long as the vaginal microbiota, immunity, and hormones keep preserving local homeostasis. Obviously, microbiological screening and the vaginal test still remain the most effective diagnostic tools.

Several experimental data both in vitro and in vivo, have shown multistage models of carcinogenic processes in female cervix structure. These models allowed the scientific community to classify different factors as initiators, promoters, and complete carcinogens to define phases of carcinogenesis—initiation, promotion, development, and progression. However, each one of these different phases may indeed be subdivided into multiple sub-phases according to the time frame and clinical symptoms. Accordingly, the current multistage model of carcinogenesis involves a morphological continuum

spanning from vaginal microbiota condition, grade of metabolic disorders, low immunity, grade of infection, and inflammation and hyperplasia/preneoplasia up to carcinoma. Overall the picture mainly includes the alterations of four broad categories of deficiencies regarding the inflammatory and cancer-related genes, (the presence of polymorphisms SNPs and defective DNA repair genes, the activation of specific oncogenes, the inactivation of tumor suppressors that affect cell proliferation, and the reduction/inhibition of genes involved in apoptosis mechanism), age, preexisting disorders, and gut/vaginal dysbiosis. During this multistep process, each neoplasm, deriving from the long-term original damaged tissue, accrues for numerous mutations and alterations that can be seen in both cancer-related genes and HPV - *C trachomatis*, which are generally considered steady silent “driver” mutations. In addition, extensive cytogenetic alterations are also frequently observed in cancer cells and both pathogens. As a result of this genomic diversity, important cellular modifications are observed, including limitless replicative potential, sustained angiogenesis, and the ability to invade and metastasize.

It is therefore not surprising that a number of outcomes essentially indicated that the proteins of oncogenic HPV and *C trachomatis* exert their carcinogenic activity by altering the functions of one or more important cellular pathways within a fertile compromised system. The mechanistic studies regarding the association of HPV and *C trachomatis* and microbiota and immunity are so far less abundant. Two important reasons for this are that: (i) the potential effectors are vastly more abundant and consequently more difficult to determine such as SNPs, age, preexisting metabolic disorders, and food/drink/smoking habits (ii) there are limited animal models available for such a scenario. However, most recent data including our hypothesis are suggestive that both HPV and *C trachomatis* associated with cancer exert their transforming activity by developing within a favorable microenvironment allowing them to maintain always active functionalities. *C trachomatis is able to* express proteins that are indeed affecting the same cellular mechanisms targeted by HPV. Therefore, what was seen as a group of unrelated effectors may now be seen together as all contributors, based on their ability to promote, and interfere at multiple level breaking down the DNA repair, proliferation, and/or apoptosis host's mechanism.

A quite substantial number of studies have suggested that a clearer picture is emerging, which explains how some cancer-associated bacteria are similar to oncogenic viruses in their transforming ability, because they also express proteins that are able to affect a number of important cellular proteins, eventually altering DNA repairs, cell cycle/proliferation and apoptosis. This in turn increases the accumulation of DNA damage, which eventually results in cellular transformation, tumor progression, and reduced response to therapy. By harnessing the knowledge acquired with the study of oncogenic viruses, it is thus likely that the precise identification and characterization of the molecular mechanism(s) of action employed by cancer-associated bacteria will contribute to further clarifying the similarities with oncogenic viruses. This will not only improve our knowledge of the origin of cancer, but it will also have preventive, diagnostic, and therapeutic implications.

Nevertheless, as a consequence, HPV and *C trachomatis both* promote oncogenesis at the very end of a long steady deteriorating silent process, which involves eventually end-up to tumor initiation, developing and/or later-stage tumor promotion and spreading, like (but not limited to) regulation of cell mutation, proliferation, apoptosis, and senescence. Indeed, different pathogens can affect different stages of tumor formation, even though the process is not virus/bacteria-specific. For the most well-known oncogenic pathways, we have briefly summarized the major identified mechanisms that affect different systems during a period of years, which promote CC initiation, formation, and development.

Meanwhile, the future of cancer therapy should also have a microbiota-based therapeutics line and shall be performed on well-defined groups of microorganisms characterizing their specific beneficial effects on the host and the recipients. Therefore, precise identification of the microbial community members in either health or in dysbiosis should be the strong theoretical foundation of future prospective research that need to focus on the interactions between the microbiome and the host's immunity as well as the interactions between age, sex, the genetic predisposition and the underlying daily habits and diet behavior in both healthy and patients. This approach will certainly raise the rate of protection against pelvic inflammatory disease and infertility and potentially will be of great help in preventing and reducing the incidence of CC.