Glycomics and Lipidopics

Extended Abstract

# Microbial dysbiosis and disease pathogenesis of endometriosis, could there be a link?

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**Abstract:**

Endometriosis is an estrogen-dependent inflammatory condition in women that is characterised by the ectopic growth of endometrial glands and stroma outside of the uterine cavity. Although there exists many theories for the pathogenesis of endometriosis, none has been successively confirmed as a direct cause for disease development. The human body comprises a diverse microflora across all tissues that can have fundamental roles in health and disease. The microbial flora in a healthy individual can vary remarkably between anatomical sites due to the physical and chemical properties of specific tissues. This includes the female reproductive tract, notably the vagina, which harbors a microbiota dominated by Lactobacilli species. In addition, a core unique microbiome has been defined for the endometrium that also includes Lactobacilli spp. In this review we examine the possibility that endometriosis could result from microbial dysbiosis, whereby significant changes to the natural microflora within the endometrium could reduce mucosal immune regulation in this tissue with concomitant expansion of pathogenic bacteria that trigger local tissue inflammation that could perpetuate the development of endometrial disease., Endometriosis is a disorder characterised by benign, ectopic growth of estrogen-dependent endometrial tissue outside of the uterine cavity, commonly in the pelvic region. The prevalence of endometriosis is more frequent in women of reproductive age and those who exhibit pelvic pain and infertility. Endometriosis seems to be most common in women aged around 25 to 45 years . Moreover, 45 to 49% of women who presented with pelvic pain, 33% with dysmenorrhea and 42% of women aged between 25 to 34 years with infertility had endometriosis. The disorder is generally associated with dysmenorrhoea (painful menstruation), dyspareunia (painful sexual intercourse) dysuria (painful urination), pelvic pain and infertility [6-9]. In addition, risk factors for endometriosis include early menarche and late menopause, short menstrual cycle and heavy menstrual bleeding, along with prolonged exposure to endogenous estrogen and exposure to chemicals that disrupt normal endocrine homeostasis within the reproductive tract. Endometriosis can be classified based on the anatomical location of lesions and severity and this can assist clinicians with sequential treatment and management of the condition. Diagnostic methods for the early identification of endometriosis are still lacking which means that clinicians must rely heavily on invasive surgical procedures for confirmation of the disease. In addition, there a few treatment and management options for patients with endometriosis, and surgical intervention remains the main option for most patients. Curative treatments for the disease are absent and this is due mainly to a poor understanding of the cellular and molecular basis of disease pathogenesis. Several studies have attempted to measure the impact of endometriosis on the quality of life of affected women and the subsequent cost across countries and ethnicities. These studies reveal that the disease bears a significant social, physical, psychological and economic burden on those affected, given that it negatively impacts an affected woman's health related quality of life, reproductive capacity and work productivity. Severe pelvic pain is the predominant contributor to a loss of work productivity among affected women and this can greatly impede other daily activities. Endometriosis thus can have a significant negative impact on a woman's life in a multi-factorial manner which urges a closer examination of the pathogenesis of the disease. Several theories have been proposed for the pathogenesis of endometriosis, however the contribution of microbial dysbiosis to the development of the disease has been poorly examined. It is now understood that the human body has an extensive microbial flora which is established early in life and each tissue displays a unique microbial flora which is determined by both the physical and chemical properties of the individual tissue. Scientists have discovered that the normal microflora can have direct health benefits to the host and if the balance between healthy bacteria and pathogens ensues (i.e. microbial dysbiosis), this can have a direct impact on disease pathogenesis. In addition, the role of the microbiota has extended from the gut and the skin which are the two major mucosal sites of microbial inhabitation. It is now apparent that the microbiota plays an important role in both health and disease in humans and can impact on various body tissues, to the extent that is has been implicated in diseases such as type 2 diabetes, autoimmune diseases like rheumatoid arthritis and multiple sclerosis and for metabolic diseases such as kwashiorkor. This review will provide an overview of some recent studies which have examined the

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makeup of the microbial flora of the female reproductive tract but also explore how microbial dysbiosis could provide a link to the development of endometriosis. Disease Pathogenesis: Endometriosis is identified as a complex disease given that it lacks a clear process of disease pathogenesis, which subsequently impedes on diagnosis and treatment. The most-widely supported theory for disease pathogenesis of endometriosis is that of retrograde menstruation .This theory supports the notion that during the normal process of menstruation, there is a reflux of endometrial tissue and cells through the fallopian tubes to the ovaries, where it subsequently enters into the peritoneal cavity and grafts ectopically to genitourinary tissue in the peritoneal cavity. Burney and Giudice explained that menstrual blood is quite commonly found in the peritoneal fluid of healthy women and this can be a common occurrence in adolescent girls with congenital outflow obstruction. Moreover, retrograde menstruation has been induced in non-human primates, the *Papio anubis* baboon, through supracervical ligation, which resulted in histologically-confirmed endometriosis. However, in challenge to the retrograde flow theory, it is observed that approximately 90% of women are known to exhibit retrograde menstruation, whilst only 15% of women have endometriosis. This implies that there are other factors that contribute to the pathogenesis of the disease. Thus, given that the retrograde menstruation theory is not conclusive, many other theories have been hypothesised. These include the stem cell implantation theory, the coelomic metaplasia theory and the Müllerian remnant abnormalities theory summarised in. Although these theories are supported to a degree by scientific evidence, they lack an absolute association to the development of endometriosis. Despite these proposed theories, a clear definite pathogenesis of endometriosis has yet to be established. Endometriosis is characterised as an inflammatory condition, given that the peritoneal fluid of women with the disease has a heightened number of activated macrophages, as established through immune-histochemical analysis of endometrial tissue, plasma and peritoneal fluid among women with and without endometriosis. Further associated to the inflammatory-state of endometriosis is an increase in a range of soluble mediators including: Chemokines: Macrophage inhibitory factor (MIF), MCP-1, RANTES [Proinflammatory cytokines: TNF-α, IL-6, IL-1β, INF-γ IL-8, IL-9, IL-17. Growth factors: Platelet-derived growth factor (PDGF), nerve growth factor (NGF) and fibroblast growth factor (FGF), also angiogenic and neurogenic factors, G-CSF. Increased nuclear factor kappa beta (NF-kB) activation has been observed in peritoneal macrophages and peritoneal endometriotic lesions of patients with endometriosis resulting in up-regulation of inflammation and cell proliferation and down-regulation of endometrial cell apoptosis. Genome-wide association studies have established certain single nucleotide polymorphisms (SNPs) associated with the disease, namely those found on chromosomes near *Wnt4, Greb1, Vezt* and *Kdr* genes as summarised. How these putative susceptibility genes impact on the establishment of ectopic tissue growth or on the immune inflammatory responses within the affected individual is currently not understood. With significant correlations found between SNPs and endometriosis, genetic factors are regarded as important contributors to the development of the disease.Animal Models of Endometriosis_One of the major barriers to understanding the cellular, molecular and genetic basis of disease pathogenesis for endometriosis is the lack of a suitable animal model. Non-human primates have been used extensively as a model of the disease and as preclinical models, due to their spontaneous development of endometriosis. Moreover, endometriosis can also be established in non-human primates through the induction of retrograde menstruation. Non-human primates are considered the most suitable model for the study of endometriosis, yet there are ethical and high-cost limitations that limit their use. Murine models offer an alternative for the study of endometriosis as they are more cost-effective and easily maintained. However, mice are unable to develop endometriosis spontaneously as they lack the ability to menstruate. In order to replicate the disease in mice, recipient endometrial tissue must be introduced into mice, either from syngeneic animals or through xenogeneic donor tissue. However, recent discoveries have identified the spiny mouse (*Acomys cahirinus*) as the first rodent species known to menstruate spontaneously, with subsequent cyclic endometrial shedding and repair. This provides a more suitable, yet still accessible and cost-effective murine model for the future study of endometriosis.

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