Endometriosis and Susceptibility to Cancer: The Dark Side of IFN-γ Gene Polymorphism?

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Endometriosis is a chronic condition characterized by the growth of endometrial-like tissue outside the uterus [1]. The prevalence of endometriosis has been connected with ethnicity in a range of potential genetic and environmental risk factors. Endometriosis generally follows a benign course [2]. However, it is at risk for transforming and becoming cancer [2-5]. Endometriosis, like cancer, is characterized by pathogenic mechanisms such as cell invasion, unrestrained growth, decreased apoptosis and development of new vessels from the existing vasculature in a process called angiogenesis [3]. In spite of these similarities, endometriosis is not described as a malignant condition [3]. The possibility that endometriosis could evolve in cancerous transformation has been postulated in the literature since 1925 [3]. To date the exact molecular mechanisms that may lead to the malignant transformation of endometriosis have not been fully defined [4]. Data have suggested that mutations in the PTEN (phosphatase and tensin homolog deleted on chromosome 10) gene may play an important role in the cancerous transformation of endometriosis [4-7]. PTEN is a tumour suppressor commonly mutated in many human cancers [8]. Progressive loss of PTEN or accumulation of mutations in the PTEN gene has been related to advancing cancer [7]. Conversely, overexpression of PTEN has been linked to the suppression of tumorigenicity and cell growth [7,8]. In addition, it has been reported that racial disparity in the frequency of PTEN mutations may contribute to the ethnic differences in cancer survival [6]. It has been found that PTEN acts as a tumour suppressor by directly antagonizing the activity of phosphoinositide 3-kinase (PI3K) pathway [7,8]. The active form of PI3K is an oncogene [7,8]. AKT and mTor are important downstream targets of PI3K*. Amplifications and mutations of PI3K have been connected with the most common human cancers [7-9]. It has been shown that mutations in the gene encoding the p110α subunit of PI3K is a downstream target of epidermal growth factor receptor (EGFR) through the mitogen-activated protein kinase (MAPK) signaling pathways [10]. Indeed, its overexpression is able to preserve cell viability in presence of EGFR inhibitors [10]. Intriguingly, it has been proved that EGFR functional polymorphism may influence cancer prognosis through an EGFR/EGFR pathway [11]. Similarly to EGFR, PI3K is also activated by EGFR [9]. Interestingly, a crosstalk between MAPK and PI3K has been proposed in cancer [12]. Prolonged MAPK activity has been associated with interferon-γ (IFN-γ) [13]. That is a cytokine whose biological activity is conventionally related to cytostatic/cytotoxic and antitumor mechanisms during cell-mediated adaptive immune response [13]. However, it has been found that IFN-γ may also have protumorigenic effects under certain circumstances [14]. In this context, it has been shown that IFN-γ gene polymorphism may contribute to cancer susceptibility [15]. Oncogenic activation evokes mechanisms to escape immune surveillance by a process called immune editing which provides a selective pressure in the tumour microenvironment leading to malignant progression [16]. In this respect, IFN-γ resistance is considered critical for cancer cell growth and survival [16,17]. Notably, it has been shown that PI3K/AKT alone mediates the IFN-γ resistance [17]. What is more, reduction of PTEN activity seems to be essential for IFN-γ resistance and hyperproliferation of cancer cells [17]. Interestingly, it has been demonstrated that enhanced lymphocyte interferon (IFN)-γ may influence the PI3K/mTor causal molecular pathway in a PTEN mutation-negative cancer syndrome [18]. It is widely accepted that endometriosis is a chronic inflammatory process with abnormalities in IFN-γ production [1,19,20]. IFN-γ gene polymorphism has been linked to different stages of endometriosis with interethnic differences across many countries [19,20]. Intriguingly, endometriotic cells are resistant to IFN-γ-induced cell growth inhibition and apoptosis [21]. Although the precise mechanism leading to IFN-γ resistance is still unidentified, it has been supposed the existence of dysregulation of intracellular signaling pathways in endometriotic stromal cells [21]. On this regard, IFN-γ has been described to activate EGFR system and to modulate EGFR activation of downstream signaling pathways [22]. The expression of EGF system in eutopic endometrium from women with endometriosis varies from healthy women with important quantitative and qualitative differences [23]. It has been provided the direct evidence of the dependence of IFN-γ-induced EGFR transactivation upon EGFR expression level in epithelial cells [24]. VEGF has also been strongly associated with the pathophysiology of endometriosis [25]. IFN-γ is considered an indirect inducer of angiogenesis through the activation of VEGF [26,27]. In particular, IFN-γ has been reported to regulate VEGF production by endometrial stromal cells in a dose-dependent manner [27]. EGR1 has also been related to endometriosis [28]. Interestingly, it has been demonstrated that IFN-γ may regulate EGR1 gene expression [29]. Intriguingly, MAPK signaling pathway has been involved directly in regulating the pathogenesis of endometriosis [30,31]. Attractively, IFN-γ has been correlated with MAPK that has been reported to exert influence on both PI3K and EGR1 [10,13]. Taken together, we speculate

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Received May 26, 2013; Accepted July 18, 2013; Published July 22, 2013


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that susceptibility to cancer in endometriosis may be correlated with ethnicity-related IFN-γ gene polymorphism that deregulates the functional network of suppressor factors that serve to maintain normal growth regulation. We advance the hypotheses that IFN-γ gene polymorphism may mediate PTEN activity deregulation, independently of the type of PTEN mutation, via upregulation of PI3K pathway and downregulation of EGFR1 through MAPK. Furthermore, IFN gene polymorphism may influence EGFR and may be responsible for the VEGF-mediated neovascularization pathway involved in the pathogenesis of endometriosis and cancer. All these contentions led us to suppose that downstream signaling pathways induced by IFN-γ variants may display multiple nodes of interaction with each other implying that perturbation of any of the tumor suppressors may cause some degree of dysfunction of the others resulting in the molecular differences in the setting of severe versus mild endometriosis and in the malignant transformation of endometriosis. IFN-γ gene polymorphism should be assessed as well as its geographic and population heterogeneities due to racial admixture. The use of racially determined polymorphisms of IFN-γ gene as biomarkers of neoplastic transformation in genetic counseling screening might provide an opportunity to identify women with endometriosis at increased risk of cancer. For women with an allele associated with cancer development and progression, knowing that they have such a mutation may be helpful in order to adopt prevention strategies from adolescence to adulthood. Furthermore, a more detailed understanding of IFN-γ/PI3K/EGFR-1/PTEN signaling axis may represent a target for the development of novel diagnostic and therapeutic strategies for both endometriosis and cancer worldwide. Genomic and proteomic studies are needed to clarify the components of the potential machinery leading to cancer by IFN-γ gene polymorphism in endometriosis.

References