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Getting Endometriosis: A Machinery Ruled by Gene Polymorphism and Epigenetic Mechanisms

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ABSTRACT

We hypothesize that endometriosis may be caused by a machinery ruled by gene silencing and epigenetic mechanisms involving EGF, survivin, telomerase and Hox genes.

Key words: Endometriosis, survivin, EGF, telomerase, Hox genes

Endometriosis is defined as the presence of endometrial tissue outside the uterus, predominantly on the ovary and pelvic peritoneum (Watanabe *et al.*, 2009). It is a common gynecologic syndrome that causes infertility and pelvic pain, compromising quality of life (Sampson, 1940; Hapangama *et al.*, 2008; Watanabe *et al.*, 2009; Zanatta *et al.*, 2010). Its pathogenesis has not yet been fully elucidated. Out of various theories put forward to explain the pathogenesis of endometriosis, Sampson's theory of retrograde menstrual reflux has gained the widest acceptance (Sampson, 1940; Zanatta *et al.*, 2010). However, it has yet to be established why some women get endometriosis whereas, others do not. Although, there is evidence that retrograde menstruation occurs in up to 90% of women, the prevalence of endometriosis in the general population is around 5-15 and 40% of women seeking infertility evaluation (Sampson, 1940; Hapangama *et al.*, 2008; Watanabe *et al.*, 2009; Zanatta *et al.*, 2010). Recent data have suggest that the eutopic endometrium of women with endometriosis seems to differ from that in healthy women (Hapangama *et al.*, 2008; Watanabe *et al.*, 2009). Endometriosis seems to be characterized by the presence of endometrial cells with capacity to avoid apoptosis beyond the uterine cavity (Hapangama *et al.*, 2008; Watanabe *et al.*, 2009), Apoptosis plays an important role in maintaining tissue homeostasis by striking a balance between proliferation and cell death (Watanabe *et al.*, 2009). A strong relationship seems to exist between the altered apoptotic machinery and enhanced survival of endometriotic cells outside the uterine cavity (Hapangama *et al.*, 2008; Watanabe *et al.*, 2009). Endometriotic cells have been described to have the peculiar biological characteristic of resistance to apoptosis with the inability to transmit apoptotic signal and the ability to avoid cell death (Sampson, 1940; Hapangama *et al.*, 2008; Watanabe *et al.*, 2009; Zanatta *et al.*, 2010). Although, normal epithelial cells undergo apoptosis when they separate from their primary tissue, spontaneous apoptosis of ectopic endometrial tissue is impaired in women suffering from endometriosis (Hapangama *et al.*, 2008; Watanabe *et al.*, 2009). Eutopic endometrium from women with endometriosis has increased expression of anti-apoptotic factor and decreased expression of pro-apoptotic factors in comparison with endometrium from healthy women (Watanabe *et al.*, 2009). Among the inhibitors of apoptosis, survivin seems to be closely linked to escape from

apoptosis of endometriotic cells and their viability with a critical role in the pathogenesis and progression of endometriosis (Watanabe *et al.*, 2009). Survivin is a protein prominently expressed in embryonic and fetal tissues and over-expressed in virtually all tumour types that seems to protect cells from apoptosis suppressing primarily caspases (Zhihong *et al.*, 2006; Watanabe *et al.*, 2009). It is transcriptionally silent in most differentiated adult tissues but it is expressed in ovary and in the proliferative phase of the cycling human endometrium evoking a physiological role in normal endometrial function (Zhihong *et al.*, 2006; Watanabe *et al.*, 2009). Recently, it has been reported that endometriosis is also associated with aberrant endometrial expression of telomerase and increased telomere length in the luteal phase endometrium with alterations in cell fate (Maida *et al.*, 2002; Hapangama *et al.*, 2008). Telomeres are non-coding tandemly repeated DNA sequences that are vital for maintaining chromosomal integrity and cell stability (Hapangama *et al.*, 2008). The critical shortening of telomeres is correlated with cells division and their senescence and apoptosis (Maida *et al.*, 2002; Hapangama *et al.*, 2008). Telomerase can prevent telomere shortening and its activation allows the cells to overcome replicative senescence and to obtain immortal capacity (Hapangama *et al.*, 2008). Intriguingly, over-expression of survivin has been related to enhanced telomerase activity (Endoh *et al.*, 2005). It has been found that both survivin and telomerase may be regulated by Epidermal Growth Factor (EGF) via Mitogen Activated Protein Kinase (MAPK) signaling pathways (Maida *et al.*, 2002; Zhihong *et al.*, 2006). The EGF system comprises four receptors, HER1-4 and several ligands and it is cyclically expressed in endometrium from healthy fertile women (Ejskjaer *et al.*, 2009; Araujo *et al.*, 2011). There are quantitative and qualitative differences in the EGF system in endometriotic eutopic endometrium compared to endometrium from healthy women (Ejskjaer *et al.*, 2009). What's more it has been reported a functional polymorphism of EGF associated with a striking ethnic heterogeneity of EGF genotype (Araujo *et al.*, 2011). A recent study has described an unexpected HOX transcriptional mechanism with permissive regulation of EGF secretion (Li-Kroeger *et al.*, 2008). HOXA10 and HOXA11 genes, encoding homeodomain transcription factors, are dynamically expressed in endometrium regulating endometrial growth, differentiation and implantation (Taylor *et al.*, 1999; Watanabe *et al.*, 2009). Although, in several cases HOX genes have a morphogenetic role, their activity is generally tightly linked to multiple signaling pathways (Taylor *et al.*, 1999; Watanabe *et al.*, 2009). Altered expression of HOXA10 and HOXA11 genes has been reported in endometriosis (Taylor *et al.*, 1999). With respect to the above discussion we hypothesize that endometriosis may be caused by a machinery ruled by gene silencing and epigenetic mechanisms involving EGF, survivin, telomerase and Hox genes. Advances in understanding specific signaling pathways at cellular level may explain why sloughed endometrium expelled into the peritoneal cavity via retrograde menstruation has enhanced replicative capacity and the ability to persist and grow in an adverse environment promoting the development of new therapeutic strategies for endometriosis.

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