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Reducing Ovarian Cancer Development in Patients of Endometriosis

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Although endometriosis is a benign condition, the presence of endometriosis has been associated with the development of various types of cancers, that include ovarian cancers. Endometriomas or ovarian endometriotic cysts, are present in 17-44% of patients with endometriosis, and might be a common precursor lesions to ovarian cancers. Endometriosis –associated ovarian cancers have been elucidated, including the dominance of certain cytokines, oxidative stress, and a hyper-estrogenic hormonal milieu, that propagate both endometriosis, and endometriosis associated ovarian cancers. Further genetic mutations including PTEN, PIK3CA, ARIDIA, Wnt/β-catenin, microsatellite instability, Src and KRAS have been shown to be critical in the pathogenesis of Endometriosis –associated ovarian cancers [1].

Early detection and accurate diagnosis are pivotal in the management of Endometriosis –associated ovarian neoplasms (ERON's), still there is no clear common ground regarding their pathogenesis. Endometriosis is a destabilising pathology which profoundly impairs the quality of life. Though the spontaneous resolution of Endometriosis is possible, studies suggest that it can be a progressive condition. Till now the gold standard for diagnosis has been an invasive method of laparoscopy followed by histological confirmation. Recently novel biomarkers have been discovered. Micro RNA's represent important epigenetic modulators of gene expression and are very attractive as biomarkers in view of their lower complexity, tissue specificity, and stability in bodily fluids. Various studies have advanced the possibility of miRNA's becoming potential biomarkers in Endometriosis and ERON's. Thus Alexandru Moga., *et al*. reviewed studies regarding miR's and found 8 miR's like miR-200 family, miR-143, miR-145, miR-20a, and miR 199a were the most commonly dysregulated miRNA's in Endometriosis, and miR-200 family was found to be dysregulated in both ERON and Endometriosis. Thus no single miR was considered as a sole biomarker for this pathology. However, since the prognostic value of biomarkers is generally enhanced if more are assessed at the same time, a panel of miRNA could be a better indicator of disease [2] (Figure 1).

Figure 1: Courtesy ref no. 2 The mechanism of the progression of endometriosis to endometriosis-related ovarian cancer. The process is initiated by heme and iron-mediated oxidative stress, leading to chronic inflammation and repeated hemorrhage. The oxidative stress produces alterations at the DNA level. These free radicals species are generated by an integrated antioxidant defense mechanism, and their production is a prerequisite in modulating different biochemical functions. During the malignant transformation of endometriosis, estrogen receptor (ER) down-regulation is observed. Loss of estrogen function, loss of heterozygosity (LOH), and the mutation of other specific genes represent the trigger factors for the switch from endometriosis to endometriosis-related ovarian neoplasms (ERONs). Additional genes, such as ARID1A, abnormalities, or other molecular alterations may lead to the progression towards ovarian cancer.

Nodal, a member of the transforming growth factor β(TGFβ) superfamily, playsa vital role in differentiation of the endoderm and mesoderm during embryogenesis [3]. Nodal expression is commonly absent in differentiated tissues [4], while its re-expression occurs in a variety of human malignancies. However, published data regarding its functional roles in tumor development and progression are conflicting. For e.g. inhibition of Nodal signaling reduces cell invasiveness, colony formation, and tumorigenicity in melanomas [5], while overexpression of Nodal reduces cell invasiveness in the number of metabolically active cells in ovarian epithelial carcinoma (OECa) [6]. Thus the role of Nodal might be dependent on the tumor cellular microenvironment and associated cell type. In a study by Miura., et al. regarding the regulation and function of Nodal and its associated molecules, including Smad3, GSK-3β and several cell kinetic –related molecules, were assessed using clinical samples consisting of 108 ovarian carcinomas and 33endometriotic lesions, along with ES-2 (ovarian clear cell carcinoma; OCCCa) and Ishikawa (endometrial carcinoma cell lines). Nodal expression was significantly higher in Endometriosis and OCCCa lesions as compared to that of non-OCCCas, with positive correlation to phosphorylated forms of both Smad2 (pSmad2) and GSK-3β. When compared to endometriotic lesions, the expression of Nodal and pSmad2 was significantly reduced in OCCCa. Treatment of Ishikawa cells with TGFβ 1 resulted in transcriptional upregulation of Nodal, along with increased pSmad2 expression while inhibition of GSK-3β also induced an increase in Nodal expression at the post translational level. Both ES-2 and Ishikawa cells stably overexpressing Nodal had increased susceptibility to apoptosis in response to treatment with cisplatin and doxorubicin, respectively, together with higher cleaved caspase-3 expression and decreased Bcl2/Bax ratio. Further the stable Nodal –over expresing cells demonstrated cell proliferation, along with increased expression of $p27^{kip1}$ and $p21^{waf1}$ in clinical samples, a significantly higher number of apoptotic cells and lower Ki-67 labeling indices were observed in Nodal-positive as compared to Nodal negative OCCCa (Figure 2). These suggested that Nodal is a multifunctional cytokine involved in the modulation of cell kinetics in ovarian –endometriosis-OCCCa lesions [7].

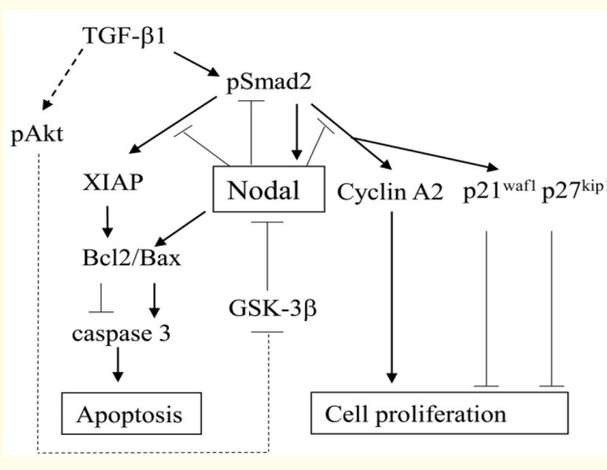

Figure 2: Courtesy ref no-7. Schematic representation of association of Nodal with susceptibility to apoptosis and cell proliferation in endometriosis- OCCCa.

Further once developed Jo., *et al*. did not find any effect of the presence of endometriosis in the prognosis of OCCC and Endometroid carcinoma [8].

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