

Title: The Expression of the EGF-system in the Endometrium. Normal Endometrium, Endometriosis and Endometrial Cancer.

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Defence: April 19th 2006, Århus University Hospital

Abstract:

The aim of the study is to describe the expression of the EGF-system in the endometrium during the menstrual cycle in healthy pre-menopausal women and in healthy post-menopausal endometrium, in endometrium from women with endometriosis and in endometrioid endometrial cancer as we hypothesised that the EGF-system play a role for normal, benign and malignant growth in the endometrium.

The Epidermal Growth Factor (EGF)-system is ubiquitous in human organs and plays fundamental roles in embryogenesis, proliferation and differentiation. It comprises four receptors, HER1, HER2, HER3 and HER4, and 12 ligands or binding-proteins divided into three groups. One of these groups includes amphiregulin, TGF- α , Heparin-Binding-EGF, betacellulin, epiregulin and EGF.

The four receptors and six ligands mentioned above was measured by real-time PCR and visualised by immunohistochemistry in human tissue samples. The samples comprise 42 endometrial samples from 14 healthy pre-menopausal and endometrial samples from 13 healthy postmenopausal women, from 23 women with endometriosis and 45 women with endometrioid endometrial cancer. From women with endometriosis we also examined samples of ectopic origin.

Based on samples from proliferative, early secretory and late secretory phase from the pre-menopausal women we describe the EGF-system as a growth factor system undergoing cyclical variation. These variations are seen in all receptors and two of the ligands, AR and TGF- α . Immunohistochemistry located the receptors to the epithelium and glandular cells, while the ligands were located to both stroma and epithelium, but also for some of them to other cells types.

Samples from women with endometriosis revealed a different pattern of expression of the EGF-system in the eutopic endometrium compared to healthy pre-menopausal endometrium. The result is interesting because it adds to the theory of endometriosis as a disease of the endometrium. A feature not described earlier, was a strong HER2 staining of some glands in the eutopic endometrium. Apart from this, no difference in staining pattern was seen compared to healthy pre-menopausal endometrium.

In the samples from women with endometrioid endometrial cancer the expression of the EGF-system showed a third pattern. Whilst in endometriosis the expression of the receptors was increased, the receptor expression in endometrioid endometrial cancer was decreased for HER1 and HER3, and increased regarding HER4 and the ligands AR and TGF- α . By immunohistochemistry the receptors were located to the epithelium, and the ligands primarily to the stroma and/or the epithelium.

In conclusion we describe for the first time the expression of all receptors and six ligands of the EGF-system in human endometrium, both under normal conditions, and after transformation in benign or malignant direction. We describe a cyclical variation, and alterations in the expression pattern under benign and malignant transformation.