

Endometriosis: A History Written by Aberrant Hoxa10 Gene Expression and Epidermal Growth Factor (EGF) System Polymorphism?

Endometriosis is a gynecologic disorder characterized by the presence of viable, extrauterine endometrial tissue, predominantly on the ovary and pelvic peritoneum (1–3). Typical symptoms consist of pelvic pain, dysmenorrhea, and infertility (1, 2). This condition takes place only in women of menstrual age, can grow or bleed cyclically and may cause adhesions (1, 2). Endometriosis represents a worldwide social disease compromising quality of life (1, 2).

The prevalence of endometriosis approaches 6% to 10% in the general female population of reproductive age, 50% to 60% of women and teenage girls with pelvic pain, and up to 50% of women with infertility (2, 3). The mechanisms responsible for the disease have not been fully elucidated yet. Therefore, the etiology of the disease is a motivation for research.

Epidermal growth factor (EGF) system has been strongly related to the regulation of the cyclical growth and shedding of human endometrium (2). A functional polymorphism of EGF system related to genotypic heterogeneity has been described (4). Intriguingly, the expression of EGF system in eutopic endometrium from women with endometriosis varies from the healthy women with significant quantitative and qualitative differences (3). In addition, a recent study demonstrated a dysregulation of EGF system in the setting of severe versus mild endometriosis suggesting functional and biochemical dissimilarities between these two types of endometriosis (5).

EGF secretion has been linked to HOX genes transcriptional mechanisms implying that homeotic genes have a permissive role in controlling EGF gene expression (6). HOX genes, encoding homeodomain factors, are crucial for embryonic morphogenesis regulating a battery of downstream genes essential for growth and differentiation (7). Although they have a morphogenetic role in several cases, their activity is generally tightly connected with multiple signaling pathways (6, 7). HOX genes were initially considered to be expressed only during the embryonic development (7). However, they have been persistently revealed in the reproductive tract (6). In addition, human

endometrium is dynamically regulated by the expression of HOXA10 gene that seems to be necessary for endometrial growth, differentiation and implantation (7). Interestingly, it has been reported that HOXA10 gene expression is altered in the endometrium of women suffering from endometriosis (6). Similarly, in a baboon endometriosis model, HOXA10 gene expression was down regulated in eutopic endometrium (8). All these contentions led us to hypothesize that aberrant HOXA10 gene expression may account for genetic variants with inter-ethnic differences in EGF system. Research studies are needed to delve deeper into the individual susceptibility to endometriosis from ethnicity-related gene polymorphisms. Specific signaling pathways between HOXA10 gene and EGF system at cellular level should be better defined in order to target new individualized racial therapeutic strategies for infertility, dysmenorrhea and pelvic pain. In this respect, a gene therapy approach involving the manipulation of HOXA10 gene expression may have important functions in prospective preventive management of endometriosis.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Giudice LC. Clinical practice. Endometriosis. *N Engl J Med.* 2010;362(25):2389-98.
2. Ejskjaer K, Sorensen BS, Poulsen SS, Mogensen O, Forman A, Nexo E. Expression of the epidermal growth factor system in human endometrium during the menstrual cycle. *Mol Hum Reprod.* 2005;11(8):543-51.
3. Ejskjaer K, Sorensen BS, Poulsen SS, Mogensen O, Forman A, Nexo E. Expression of the epidermal growth factor system in eutopic endometrium from women with endometriosis differs from that in endometrium from healthy women. *Gynecol Obstet Invest.* 2009;67(2):118-26.
4. Araújo AP, Catarino R, Ribeiro R, Pereira D, Pinto D, Medeiros R. Epidermal growth factor genetic variation associated with advanced cervical cancer in younger women. *Am J Clin Oncol.* 2012;35(3):247-50.

5. Aghajanova L, Giudice LC. Molecular evidence for differences in endometrium in severe versus mild endometriosis. *Reprod Sci.* 2011;18(3):229-51.
6. Li-Kroeger D, Witt LM, Grimes HL, Cook TA, Gebelein B. Hox and senseless antagonism functions as a molecular switch to regulate EGF secretion in the *Drosophila* PNS. *Dev Cell.* 2008;15 (2):298-308.
7. Zanatta A, Rocha AM, Carvalho FM, Pereira RM, Taylor HS, Motta EL, et al. The role of the Hoxa 10/HOXA10 gene in the etiology of endometriosis and its related infertility: a review. *J Assist Reprod Genet.* 2010;27(12):701-10.
8. Kim JJ, Taylor HS, Lu Z, Ladhami O, Hastings JM, Jackson KS, et al. Altered expression of HOXA10 in endometriosis: potential role in decidualization. *Mol Hum Reprod.* 2007;13(5):323-32.

Raffaella Mormile ^{1*}, Giorgio Vittori ²

1- Division of Pediatric and Neonatology, Moscati Hospital, Aversa, Italy

2- Division of Gynecology, San Carlo di Nancy Hospital, Rome, Italy

* Corresponding Author: Raffaella Mormile, Division of Pediatric and Neonatology, Moscati Hospital, Via A. Gramsci, 3-81031, Aversa, Italy
E-mail: raffaellamormile@alice.it