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Commentary

Major Critical Periods in Developmental Pathogenomics of Endometriosis

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Commentary/ Editorial: In spite on numerous experimental and clinical data molecular mechanisms of endometriosis (EM) - the most common benign tumor of the female reproductive tract still remains obscure . The deciphering enigmas of EM gave a birth to a number of hypothesis [1.2.3] . System genetics approach used in our studies of common diseases support the existence of special genetic program of EM operative in its development[4]. It is taken for granted that EM results from abnormal differentiation of stem cells (SC) [5]. Two major sources of EM SC are considered : SC disseminated throughout peritoneum during female reproductive organs embryogenesis [1], SC from junction zone the uterine endometrium (2) [6]. According to our reviewed hypothesis [7] the genetic program of EM consists of several critical periods (CP) [8] corresponding to three crucial events in EM development with each of them corresponding to major genome reprogramming in EM cells [9].

CP-1 (antenatal) hits the embryonic development of female reproductive organs It starts on the 6th week of gestation and proceeds to early postnatal life. The cells of Mullerian ducts and splanchnopleura disseminated within peritoneal cavity may stay dormant in postnatal mesothelium until provoked t tumorogenesis by external toxins and abnormal genetic factors [4]. Mutations or functional insufficiency of *HOX10A* , *WNT-4* genes as well as the genes of their cascades (*MIF*, *VEGF*, *MMPs*. *VCAM*, *BMP e*tc) cause disorganization of endometrium as well as SC dissemination of mesothelium incorporating outside uterine cavity and initiate inherited (inborn) predisposition to disease. EM with inherited impairments of WNT-4 or HOX 10 genes gives a rise to more sever forms of EM than EM of mostly epigenetic by its origin [3,10] Thus CP 1st most probably results from unfavorable combination of EM predisposition genes (predominantly of WNT and HOX families) , noxious agents (oxidative stress, pesticides, endocrine disruptors) might favor conditions for differentiation, adhesion, proliferation and survival of eutopic and ectopic endometrial SC. Direct association of unfavorable WNT-4 allele with EM has been recently demonstrated [10,11].

CP- II concerns epithelia – mesenchymal transition (EMT) and metaplasia of pelvic epithelia cells into EM cell. EMT means the conversion of otherwise polarized epithelium cells through several consecutive divisions into mesenchymal SC . EMT is considered the most plausible mechanism responsible for the formation of the EM lesions.[12] Its staging is studied in details starts as a suppression of cadherine H1 gene by the gene TWIST stimulated by transient hypoxia and mechanic transduction by environmental pollutants, hormonal imbalances, proliferation induced by MYC & FGF genes. It is also supported by many relevant genes (*HIF2 TWIST; TGFβ; WNT, MMP,BCL2,VZT).* EMT gives a rise to me-SC, induce proliferation, loss of intercellular contacts , migration into peritoneal cavity . Junctional zone at the boundary of endometrium and mesometrium where me-SC have the best natural nicha for SC of endometrium thus also for endometriosis[13].

CIII corresponds to the peritoneum invasion, proliferation and differentiation of the EM SC carried in the mensis blood wastages in pelvic cavity , implant or transform into EM. All these pathological changes occur because of decreased cellular immunity, reduced natural killer cells , absence of cell clearance in peritoneal cavity . The mesenchymal - SCs produce inflammation , recruit macrophages & promote EM. The genes participating in CIII facilitate proliferation, implantation are and well studied D numerous ysfunctional expression of the genes related to the Mullerian embryogenesis (see SPh 1) as well as epigentic immuno-endocrine deregulation of the genes in endometrium (*IL11*, *LIF*, *TGF-beta*, *FKBP4*, *COX2*, *PGs*, *FOhO1* and *C/EBPbeta*) might appear critical to the development of endometriotic lesions\(EML) [14.15].

Significant changes in lipid metabolism ADH1B , FABP4 PLA2G2A have been also recently found in the otherwise normal peritoneal cells of EM affected women as well as in the cells of endometrioma . The evolvement of these genes in metaplasia of pelvic cells or activation of dormant mesothelial cells of embryonic origin was suspected [16]

To a summary: EM is guided by its own developmental program, through the major genetic and epigenetic changes of the numerous gene nets impairment of SC of different origin [12]. Equifinality of pathologic events in EM affected females is determined by genome peculiarities as well as by unique epigentic landscape of each affected woman. MDP postulates development of EM from SC of uterine endometrium and also from embryonic SC cells of Mullerian rests disseminated throughout the cavity during embryogenesis of female reproductive tact (FRT) . EMDP includes at least 3 sensitive (critical) periods. One - prenatal (8-10 w.g.) coincides with critical embryonic period of FRT development and 2 - postnatal: endometrial - mesenchymal transition (the 2nd) invasion of SC, and the growth of endometrioid lesions (the 3rd). According to developmental genetics postulates[7,8] suggested CPs most probably-correspond to the periods of massive reprogramming of meSC genome expression and basic changes of EMDP check points. CP hypothesis provides an ample opportunity for the search of novel EM biomarkers as well as for elaboration more efficient predictive strategy for its personalized treatment Validity of DPEM could be checked by means of correlation studies of EM frequencies with feasible teratogenic effects of noxious agents producing retardation during early pregnancy (1st trimester(;frequency of EM with mutation of genes responsible for early stages of female reproductive system development; also by analysis of EML as feasible miniteratomas derived from meSC while getting from uterus inside peritoneal cavity .

Conflict of Interest

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