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Cell biology of nascent endometriosis implants

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Context – Endometriosis is a non-malignant, but metastatic, condition manifested by the extrauterine growth of inflammatory endometrial implants. The etiology of endometriosis remains controversial. While neonatal seeding of lesions and adolescent onset of symptoms are increasingly recognized, the factors involved in their development and progression are unknown.
Objective – To understand the phenotype of early lesions, our laboratory has pursued the hypothesis that innate immune cells stimulate "neuroangiogenesis", a process that coordinates the functional innervation, vascularization and ultimately growth of endometriosis lesions.
Methods – Antibody microarray analyses and immunohistochemistry identified Brain-Derived Neurotrophic Factor (BDNF) within glands and stroma of the lesions. Primary human endometrial stromal cells (ESC) were established and assessed by Western blots.
Participant(s) – Eight subjects with endometriosis and pain were studied.
Intervention(s) – ESC were stimulated with IL-1? in vitro to mimic the effects of macrophage-derived cytokines in vivo.
Main Outcome Measure(s) – Temporal and dose-dependent effects of IL-1? on BDNF expression were established and pathway mediators were identified.
Result(s) – IL-1? potently (IC50~5 ng/ml) stimulated expression of pro- and mature BDNF protein isoforms in ESC. Inhibitors of NF-?B and c-Jun N-terminal kinase (JNK) indicated that these were the major pathways activated by IL-1?.
Conclusions – The findings support the theory that macrophage paracrine factors (eg, IL-1?), can promote neuroangiogenesis via inflammatory signal transduction pathways that include NF-?B and JNK. We propose that these factors are involved in the establishment of nascent endometriosis lesions and are potential targets for novel, non-hormonal therapies designed to retard or prevent the development of endometriotic implants in young women.

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