uPAR localization in normal cycle and endometriosis.

Mesa-Tejada, R.; Szabolcs, M.; Husami, N.; and Mazar, A.

RMT: Pathology, P&S
MS: Pathology, P&S
NH: Center of Endometriosis Treatment and Research, Columbia University, P&S
AM: Attenuon, LLC, San Diego, CA

Introduction. Increasing evidence supports a central role for the cell-surface urokinase plasminogen activator receptor (uPAR) in the regulation of pathways mediating tissue remodeling and angiogenesis. In addition to its detection and localization in various tumors, studies in eutopic and ectopic endometrium suggest its overexpression in endometriosis. To investigate uPAR as a possible clinical indicator and/or therapeutic target in endometriosis, we began with the systematic immunohistochemical detection of uPAR, with well-characterized monoclonal antibodies (Mabs), in all stages of the endometrial cycle as a prelude to its localization in endometrial lesions.

Materials & methods. E180 was selected from several Mabs produced to uPAR, by preliminary titrations on HeLa cells and endometrial carcinoma tissues, and used [at 0.2 and 0.1 μg/ml, with overnight incubation, in an automated immunoperoxidase procedure (DakoCytomation EnVision™+)]. Sections were cut from archival paraffin-embedded tissues of normal endometria [1-3 cases each: early and late proliferative, secretory (days 16-21, 23-28) and menstrual] and 14 cases of endometriosis. Two pathologists (RMT, MS) selected the tissues and interpreted the results.

Results. In proliferative endometria, uPAR localization was confined to endothelial cells in scattered vessels and capillaries and rare stromal cells. A similar distribution was seen in secretory endometria through day 25, with reaction product in glandular secretions appearing on day 24. On day 26 striking positivity (cell membrane and cytoplasmic) in pre-decidual cells was first noted, thereafter increasing in intensity through day 28, correlating with the distribution of pre-decidua in the endometrial stroma. In menstrual endometrium, these strongly positive pre-decidual cells were noted surrounding fragmented glands with variably, but clearly, positive epithelial cells, many with apoptotic features. Findings in endometriosis essentially mirrored the observations in eutopic endometria, i.e., the distribution and intensity of uPAR localization was related to the staging of the endometriotic focus. Thus, uPAR was only detected in cycling endometriosis, with significant localization in stroma that had undergone pseudodecidual change and in glands containing apoptotic epithelial cells. Inactive, fibrotic lesions had only rare positive endothelial and interstitial cells.

Conclusion. The tissue localization of uPAR in normal endometrium and endometriosis lesions is consistent with the few previous reports based on quantitative detection assays

on tissue components and fluids. The present primarily descriptive study suggests an incremental expression of uPAr concurrent with increasing progesterone effect in both eutopic and ectopic endometrial tissue components. This association requires careful analysis in light of reported quantitative data as well as treatment status of the endometriosis cases. However, the morphologic correlation allowing the identification of the cellular elements expressing uPAR provides a rational basis for effectively dissecting the function of the uPA/uPAR system in endometriosis and exploring potential clinically relevant interventions.