# Network Analysis Points to Inflammatory Protein Players in Endometriosis

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By Andrea Anderson

NEW YORK (GenomeWeb News) – A Massachusetts-based team reporting in *Science Translational Medicine* has identified an abdominal fluid protein signature that's present in a subset of individuals with endometriosis, highlighting the inflammatory processes that can contribute to the condition.

Investigators from the Massachusetts Institute of Technology and Newton Wellesley Hospital's Center for Minimally Invasive Gynecological Surgery used protein microarrays to look at levels of 50 different inflammation-related proteins in abdominal, or "peritoneal," fluid from 77 women with or without endometriosis.

In individuals with endometriosis who appeared prone to severe endometriosis-associated lesions and problems conceiving, they detected a distinctive signature involving more than a dozen immune signaling proteins known as cytokines.

That set included proteins already implicated in endometriosis as well as players from a c-Jun protein-containing stress response pathway with a less well-established role in endometriosis. It also reinforced the notion that endometriosis-associated inflammation involves enhanced activity by macrophage cells, which release many of the proteins found in the signature.

If such findings hold in follow-up studies, the team noted that it may become possible to glean prognostic insights from the signature or even treat some endometriosis patients by staunching such inflammatory activity.

"There's a great deal of interest in getting closer to [treating] the inflammatory aspects of endometriosis and we hope that this is a small step in that direction," first author Michael Beste, a post-doctoral researcher in senior author Linda Griffith's biological engineering lab at MIT, told

*GenomeWeb Daily News*.

Endometriosis is characterized by uterine tissue that creeps into neighboring organs and accumulates there, sometimes causing chronic pain and infertility. Although relatively common, endometriosis symptoms and severity can vary and the source of the condition remains poorly understood, making it tricky to decisively diagnose.

"Surgery is the de facto method for diagnosis," Beste said. "Because that's a fairly high barrier to diagnosis, it often entails significant latency between the initial onset of symptoms and the time that the patient receives a conclusive identification of the disease."

Moreover, most treatments provided prior to surgery hinge on hormone-altering compounds that curb the growth of both endometrial lesions and normal endometrial tissue, which also affects patients' chances of becoming pregnant.

Consequently, there is ongoing interest in uncovering molecular markers that might lead to more refined diagnoses and/or alternative treatment options, while providing clues to an individual's prognosis and predicted treatment response patterns.

"We would love to have more definitive techniques to work on more of a preventative timeline, where we're identifying signs, symptoms, biomarkers, and measured, objective findings that are set off very early in a woman's chronological disease history," Beste said.

For the current study, he and his colleagues focused on wide range of cytokine, chemokine, and growth factor components in peritoneal fluid, based on past studies pointing to the potential importance of peritoneal inflammation in some aspects of the disease process.

Using multiplexed immunoassays, the team quantified levels of 50 such proteins in peritoneal samples from 41 women with untreated endometriosis, 16 women with treated endometriosis cases, and 20 unaffected controls.

The researchers' multivariate analysis of the protein profiles and patient characteristics revealed enhanced activity by 13 cytokines amongst individuals with endometriosis who were less likely to have children but more likely to have developed serious lesions affecting other tissues such as the large intestine or vagina.

That collection included inflammatory compounds linked to endometriosis in the past, including components of NF-kabba B pathway. It also included components from a pathway containing c-Jun — a protein targeted by an endometriosis treatment being investigated based on findings from a drug screening study.

"What our particular analysis allowed us to do was prioritize that c-Jun finding amongst others that had been previously proposed," Beste said.

With the help of a network analysis that considered the sorts of cells known for expressing such proteins, the team saw an apparent role for macrophages in the inflammatory effects found in the same subset of endometriosis cases.

Activated forms of those immune cells, which gobble up other cells and foreign material, are known for secreting a significant proportion of the cytokines identified in the new signature. That pattern held when researchers looked at macrophage cells from patients whose peritoneal fluid contained high levels of the proposed biomarker proteins.

Even so, the study's authors noted that more research is needed to understand what prompts this particular inflammatory response in some individuals with endometriosis and how it may produce specific sets of symptoms.

The group has not yet completed longitudinal studies to look at whether the same protein set coincides with progression to more severe endometrial lesions or reduced success becoming pregnant over time, Beste said. "These are markers that one would want to look at very carefully in a longitudinal setting."

He noted the team has established collaborations with groups in Brazil and Norway, respectively, to validate findings from the current study and narrow in on markers specific to endometriosis patients experiencing fertility problems. There is interest in studying younger individuals with endometriosis symptoms over time as well, to see if particular protein profiles correspond with different disease trajectories.

Some authors of the current analysis are also considering ways of studying other conditions, such as inflammatory bowel disease, using the same sort of protein profiling and network approach.

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