Gynecology & Obstetrics
ISSN: 2161-0932

Kirma et al., Gynecol Obstet 2017, 7:11
DOI: 10.4172/2161-0932.1000e125

Editorial Open Access

Intercellular Communication, a Missing Link in Endometriosis Peritoneal Invasiveness

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Recieved date: November 10, 2017; **Accepted date:** November 13, 2017; **Published date**: November 20, 2017

Editorial

Endometriosis, a benign yet highly invasive disorder, affects about 10% of women of reproductive age and is prevalent in 30% of women with infertility. In addition to infertility, endometriosis can result in dysmenorrhea and severe abdominal pain [1]. These symptoms, acerbated by inflammation and deep infiltrating lesions, can have debilitating effects and significantly impact the well-being of women with endometriosis. It was estimated, based on 2002 data, that endometriosis has an overall associated costs of $18-22 billion, which include treatment and effects on life-style, in the United States annually [1]. Endometriotic lesions form in the pelvic cavity, where refluxed menstrual endometrial tissues invade into the peritoneum, the ovaries and other sites in the pelvic cavity. The processes involved in the invasiveness of ectopic endometrial tissue that lead to the establishment of endometriotic lesions are poorly understood. Furthermore, the cellular and molecular heterogeneity in different endometriotic lesion types and sites as well as intra-lesion heterogeneity are still underappreciated. As a result, the treatment modalities for endometriosis remain limited and include surgical intervention and hormone-based therapies, which are associated with deleterious side effects.

An estimated $44 million was spent by the NIH on endometriosis funding in the last five years (based on https://report.nih.gov/categorical_spending.aspx). While this has to be considered within the confines of the NIH total budget, it is obvious that additional research funding is needed to advance endometriosis research and to have a translational impact on clinical practice. In 2009, a report was published on the priorities for endometriosis research culminating from an international consensus workshop sponsored by the World Endometriosis Society and World Endometriosis Research Foundation [1]. Several recommendations were outlined to enhance endometriosis research focusing on diagnosis, classification and prognosis, epidemiology, and pathophysiology [1]. These recommendations included a better understanding of the role of eutopic endometrium; hormonal and non-hormonal influences, including inflammatory responses; and fostering multi-center, multidisciplinary translational and clinical approaches. Recently there have been some advances in the pathophysiology of endometriosis and in genomics approaches delineating molecular profiles [2]. Nonetheless, almost 10 years since the publication of the consensus report many of its recommendations remain to be fulfilled [1]. Efficacious, long term therapies for endometriosis are still lacking. This stagnation in the field underscores the need for integrative and multidisciplinary initiatives that use cutting edge technologies to dissect endometriotic lesion establishment and development.

A Case for Intercellular Communication Affecting Endometriotic Lesion Establishment

It has long been recognized that the molecular profiles of endometriosis are similar to those of cancer, reflecting the invasive potential of both diseases [1]. While the route and mechanisms of cellular transport to distant sites differ between endometriosis and metastasis, the establishment of lesions at distant sites requires cellular interactions with the target tissue as a pre-requisite for invasiveness. In endometriosis, lesion establishment requires initial interactions of endometrial tissue and peritoneal mesothelial cells (PMCs) followed by trans-mesothelial invasiveness. This invasive cell behavior, studied most intensively in metastasis and extravasation, involves dynamic changes in intercellular interactions [3], particularly related to cell adhesion [4] and coupling via gap junction intercellular communication (GJIC) [5]. Gap junctions are clusters of transmembrane channels formed by connexin molecules, which connect the cytoplasm of adjacent cells and mediate exchanges of ions, metabolites and signaling molecules [6]. They have been directly implicated in both extravasation [7,8] and metastasis [5,9], as well as embryonic implantation into the endometrium [10].

Our collaboration (Nicholson in gap junctions, and Kirma in endometrial cellular and molecular profiling) has integrated our expertise to address intercellular communication affecting endometriosis lesion development. We have examined the role of interactions between primary eutopic endometrial cells and PMCs, using a range of tools from single cell profiling to protein expression patterns and functional assays of GJIC and invasiveness. Endometrial cells from endometriosis patients and normal subjects showed differential GJIC, which was disproportionally modified in heterotypic interactions of patient endometrial cells with mesothelial cells. This enhanced coupling was induced by PMC-mediated paracrine feedback. The role of these cellular interactions is currently being studied with regard to endometrial invasiveness into the PMC lining. Our ongoing studies will interrogate heterogeneity at the single-cell level within endometrial epithelial and stromal cell populations in biopsies (both eutopic and ectopic) from women without and with endometriosis at different stages.

While some published studies have addressed gap junction activity and connexins expression in endometriosis [11,12], our studies open a new window into understanding cell-cell interactions in endometriotic lesion development down to the single-cell level. Our microfluidic single-cell platforms and automated high throughput microscopic functional assays have enabled us to maximize the use of primary cells from limited endometrial biopsies, by making possible multi-scale analyses from limited biopsied samples. While our initial studies focus

on cell-cell communication, these cutting-edge technologies will also be beneficial to examining many aspects of endometriosis pathology.

Acknowledgements

Our studies are supported in part by seed funding and Women's Health Initiative award from the School of Medicine, University of Texas Health San Antonio (Kirma and Nicholson) and Endometriosis Foundation of America (Kirma). Microfluidic and single-cell studies are performed by the Bioanlaytics and Single Cell Core, funded by the Cancer prevention and Research Institute of Texas (CPRIT, RP160844), and functional assays are performed at the High Throughput Screening Facility (HTSF) funded in part by CPRIT. The HTSF also receives support from the CTSA grant (UL1TR001120-01/ KL2TR001118-01/ TL1TR001119-01).

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