LABORATORY OF HUMAN REPRODUCTION

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BACKGROUND

Implantation is a progressive and versatile process in which the blastocyst apposes, attaches and finally invades the underlying endometrial surface. The uterus is ready to accept the implanting embryo only during a limited period of time known as the 'window of implantation', outside of which the endometrium may be indifferent or even hostile to the embryo. The synchronized development of the embryo to the blastocyst stage and the differentiation of the uterus to the receptive state are critical to this process. For this purpose, an effective 'cross-talk', which involves several endocrine, paracrine and autocrine factors, needs to be established between maternal and fetal tissues. In humans, the efficiency of the process is remarkably low. Once implantation begins, it has been estimated that it is successful in no more than 30% of cases. Disruption of events very early in pregnancy may be responsible for non-chromosomal pregnancy loss, which continues to be a major limiting factor in assisted reproductive therapies. Despite significant progress in reproductive research, many fundamental questions about implantation remain unanswered. The ovarian hormones have a central role in initiating the events and under their influence a complex network of molecules is mobilized at the maternal_fetal interface

RESEARCH ACTIVITIES

Research plans of the laboratory of A. Makrigiannakis include the investigation of the molecular mechanisms which are involved in the pathophysiology of implantation and placentation. Our research group has produced sufficient data to support the involvement of a network of neuropeptides, pro-apoptotic and adhesion molecules in the regulation of early trophoblast invasion and placentation. We thus intend to further explore the links between molecular biology of the implantation site and pregnancy complications, such as abortion and preeclampsia. Furthermore, our laboratory is investigating the molecular and cellular mechanisms of follicular development and corpus luteum formation and the expression, regulation and biological role of Defensins in the female reproductive system.

Specifically, the Makrigiannakis' laboratory is investigating the next specific areas of research:

1. Role of corticotropin-releasing factor (CRF) and its family molecules urocortins (UCNI, UCNII, UCNIII) in the human embryo implantation site.

The corticotropin-releasing factor (CRF) and its family molecules the urocortins (UCNI, UCNII, UCNIII) are the major regulators and coordinators of these behavioral, endocrine and immune responses of the human organism to stress. In our lab, the role of CRF and CEACAM1 peptides in the physiology of trophoblast invasion as well as the role of CRF, UCN and pro-apoptotic Fas/FasL peptides in implantation failure is currently investigating. A major effort in our lab is to examine the effect of decidual lymphocytes on extravillous trophoblasts (EVT) as a potential element of the cellular and molecular mechanisms involved in the pathophysiology of recurrent miscarriages.

2. Role of corticotropin-releasing factor (CRF) and urocortins in the pathogenesis of diseases associated with defective placentation such as preeclampsia.

Preeclampsia is a multisystem disorder that is unique to human pregnancy. Despite the widespread occurrence of preeclampsia, the underlying cause or causes of the disease remain elusive. Extravillous cytotrophoblast invasion and remodeling of the uterine spiral arteries are important aspects of normal placentation. In contrast to normal pregnancy, in pregnancies associated with preeclampsia, cytotrophoblast invasion is shallow and pregnancy-specific changes of uteroplacental arteries is absent. Besides reduced trophoblast invasion of uteroplacental vessels, preeclampsia is also associated with increased apoptosis of the extravillous trophoblast in the placental bed and increased infiltration of activated maternal macrophages around the nonremodeled spiral arteries and changes in their distribution pattern. Recently, in the pathogenesis of preeclampsia have been additionally implicated abnormalities of the placental corticotropin-releasing factor (CRF) system. The objective of our lab's project is to identify the biological basis for macrophage activation and explore the role of the Fas/FasL apoptotic pathway in preeclampsia. In addition we intend to elucidate the role for CRF in preeclampsia.

3. Molecular and cellular mechanisms of follicular development and corpus luteum formation.

The formation of the corpus luteum (CL) is critical for the establishment of a successful pregnancy. Following ovulation, under the influence of luteogenic hormones, the CL develops from the remnants of the ovulated ovarian follicle. This process involves intense reorganization of constituent cells, phenomena that includes varying cell-matrix interactions. In order to understand the role and potential regulation of cell-matrix interactions in the formation of the CL, we are currently investigating the expression of the matrix protein fibronectin (FN) and selected FN-binding integrin receptors on luteinized granulosa cells (GCs). We further are trying to examine the possible regulation of that expression by the luteogenic hormone, hCG and the involvement of mitogenic VEGF. Lastly, we aim to investigate the role of the integrins $\alpha 5\beta 1$ and $\alpha v\beta 3$ in promoting the adhesion, migration and survival of GCs.

4. Expression, regulation and biological role of Defensins in the female reproductive system.

A very important family of natural antimicrobial peptides, which are detected to a wide range of different species of organisms are Defensins. Defensins are the probable tools of a stronge mechanism of self-defense, since they act like effective immune regulators at the adoptive immune system of the selective T cells and immature Dendritic Cells (DCs). Although the role of inflammation in promoting tumor angiogenesis has been established, whether beta-defensins or DCs (their targets) are involved in these mechanisms remains unknown. Recently a new “pathogenic” mechanism is being described, supporting vasculogenesis in tumors. Data indicates that b-defensins recruit DC precursors through CCR6 into the tumor, where VEGF-A transforms them into endothelial -like cells that engage in vasculogenesis and function as promoters of tumor progression. Thus one of the main objectives of our lab is to determine whether tumor vasculogenesis involves the cooperation of VEGF-A with b-defensins.

Representative publications

1. Makrigiannakis A, Zoumakis E, Kalantaridou S, Coutifaris C, Margioris AN, Coukos G, Rice KC, Gravanis A, Chrousos GP. Corticotropin-releasing hormone promotes blastocyst implantation and early maternal tolerance. Nat Immunol 2001, 2:1018-1024.

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3. Bamberger CM, Minas V, Bamberger AM, Charalampopoulos I, Fragouli Y, Schulte HM, Makrigiannakis A (2007) Expression of urocortin in the extravillous human trophoblast at the implantation site. Placenta 2007, 28: 127-132

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5. Rolaki A, Coukos G, Loutradis D, DeLisser HM, Coutifaris C, Makrigiannakis A. Luteogenic hormones act through a vascular endothelial growth factor-dependant mechanism to up-regulate alpha5beta1 and alphavbeta3 integrins, promoting migration and survival of human luteinized granulosa cells. Am J Pathol 2007, 170: 1561-72.

Group members

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