

DBAMS fellowship PNRR

Title: Biochemical analysis of oxidative stress and pain in endometriosis

Description:

Endometriosis, a chronic condition in which the endometrium, which usually provides the inner facing of the uterus, sprouts in other areas, normally on the bowel, ovaries, bladder, rectum, and pelvic lining. Depending on the stage of the disease, it could lead to dysmenorrhoea, infertility and chronic recurring pelvic pain in billions of women of reproductive age. Retrograde menstruation is the generally accepted mechanism underlying the pathogenesis of endometriosis. This mechanism was originally proposed in 1927, whereby endometrial fragments migrate from the fallopian tubes into the peritoneal cavity during menstruation. Once the endometrial debris becomes ectopic, adhesion needs to occur in order to initiate the development of lesions and the induction of endometriosis. While the mechanisms underlying this process remain unclear, it is considered that immune dysfunction and the subsequent inability to effectively clear these fragments enables endometrial lesions to form in the peritoneal cavity. From the histological point of view, epithelial cells and stroma are capsuled in surrounding tissue and show extensive fibrosis and smooth muscle metaplasia. Lesions are characterized by invasiveness and mobility, fibroblast–myofibroblast differentiation and epithelial–mesenchymal transition. Recent findings underline the importance of the oxidative imbalance and inflammatory responses both at the lesion site and in the peritoneum and the related chronic pain state. These proinflammatory microenvironment includes inflammatory cytokines/chemokines, prostaglandins, growth factors (GR) and reactive oxygen species (ROS). In peritoneal fluid of patients, increased levels of protein oxidative stress markers, tumor necrosis factor- α (TNF- α), prostaglandin E2 (PGE2) and interleukin (IL) IL-1 β and IL-8 were found. These mediators produce activation of sensory nerve and nociceptive pathways, proposing inflammatory mechanisms may be critical in endometriosis associated pain. Further retrograde menstruations increase extra-uterine debris and lesions. The increased inflammatory answer within the peritoneum activates sensory nerves to induce chronic pelvic pain. Moreover, stimulation of sensory afferent nerves leads to the recruitment of mast cells and consequent release of the previously mentioned proinflammatory mediators, which contributes to establishing a positive feedback loop called “neurogenic inflammation”. The activation of peripheral nerve endings translates the stimuli to the spinal cord inducing central sensitization.

The theme of the project concerns the study of biochemical and molecular mechanisms for the evaluation of chronic pain related to endometriosis.

Among the natural substances, our attention was focused on snail slime. Previous studies, conducted in our laboratories, have shown that snail slime, secreted by the *Helix aspersa* Muller snail, has a strong anti-inflammatory activity, demonstrated in *in vivo* studies. The idea of using mucus or snail secretion has its roots in the history of man when in ancient times the mucus was used for the treatment of skin disorders; today it is proposed as components for the formulation of parapharmaceutical products for wound management and as a constituent of cosmetic products. Current knowledge about the mucus produced by *Helix aspersa* Muller states that mucus is rich in hyaluronic acid, mucopolysaccharides, polyphenols and bioactive minerals. These improve the adhesion of the mucus to the skin, acting as a protective barrier, while the polyphenols counteract the damage caused by oxidative stress. Furthermore, the mucus is characterized by reparative activity with emollient, antimicrobial and adhesive properties. Thanks to these characteristics, the mucus extracted from *Helix aspersa* Muller has been successfully used as a re-epithelising treatment in the management of burns in adults.

The aim of the project is to use the in vivo experimental model of chronic pain induced by endometriosis to evaluate the use of new natural substances useful in the early diagnosis of the disease and to improve the quality of life.

Period in the industry:

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The aforementioned institution will host the PhD student beneficiary of the scholarship financed on the resources of Ministerial Decree 351/2022 for no. ____6____ months (min 6 max 12) during the doctorate.

Period Abroad:

The research program provides for a period abroad of no. ____6____ months (min 6 max 18) at the following institution:

University of Roehampton

We also declare that this program complies with the principle "not to cause significant damage" (DHS) pursuant to art. 17 of regulation (EU) 2020/852 in coherence with the technical guidelines prepared by the European Commission (Communication of the European Commission 2021 / C58 / 01) and guarantees compliance with the horizontal principles of the PNRR (contribution to the climate and digital target so-called tagging, the principle of gender equality and the obligation to protect and enhance young people).