Could fibroblast senescence and resistance to apoptosis be the hidden drivers behind endometrial fibrosis in equine endometrosis?

Katarzyna Piotrowska-Tomala

Institute of Animal Reproduction and Food Research polish Academy of Sciences in Olsztyn

Fibrosis, the excessive deposition of extracellular matrix (ECM) components in organs, is a hallmark of many chronic diseases. In mares, a condition known as endometrosis, significantly reduces fertility and leads to major economic losses. Endometrosis involves changes in the mare's endometrium, such as abnormal tissue remodeling, excessive ECM production, and disruption of glands and blood vessels. Although extensively studied, current therapies are ineffective in reversing fibrosis, and the processes that drive this condition remain poorly understood.

A growing body of research highlights the critical role that senescence plays in the process of fibrosis. Senescence is a protective mechanism in which damaged cells stop dividing. However, when senescent cells accumulate in tissues, they contribute to chronic diseases by secreting molecules that drive inflammation and fibrosis. These molecules, collectively known as the senescence-associated secretory phenotype (SASP), stimulate the production of excess ECM, disrupt normal tissue function. Senescent cells are also resistant to apoptosis, a form of programmed cell death, allowing them to persist and exacerbate damage.

This research project aims to elucidate the role of senescence, apoptosis resistance and excessive ECM production in the development of fibrosis in the equine uterus. Evidence suggests that senescent fibroblasts play a central role in fibrosis, particularly by maintaining fibrotic activity, and resisting apoptosis. Recent studies have identified genes linked to senescence and apoptosis resistance in the fibrotic mare endometrium, including *NUPR1*, a transcription factor that promotes fibrosis in other organs like the kidney and lung. Excitingly, targeting *NUPR1* or using senolytic drugs (substances that selectively eliminate senescent cells) has shown promise in reducing fibrosis in laboratory models.

This study proposes three main hypotheses: (1) the number of senescent cells in the equine endometrium increases as endometrosis progresses, (2) these cells promote fibrosis by including ECM remodeling, fibroblast differentiation into myofibroblasts, (3) targeting senescent cells with senolytic drugs or inhibiting *NUPR1* can reverse apoptosis resistance and modulate processes involved in endometrial fibrosis in mares. This study proposes a complex approach involving both, *in vivo* and *in vitro* studies, as well as the use of high-throughput techniques such as RNA-Seq, LC-MS/MS, which will generate new data and provide valuable insights into the mechanisms underlying the development of endometrial fibrosis in mares during endometrosis.

A deeper understanding of the role of senescent cells and the mechanisms of apoptosis resistance may offer a promising avenue for the development of a therapeutic strategy to mitigate or reverse endometrial fibrosis in the mare. The knowledge gained from this project may inspire treatments for fibrosis in other organs and even other species, benefiting both veterinary and human medicine.