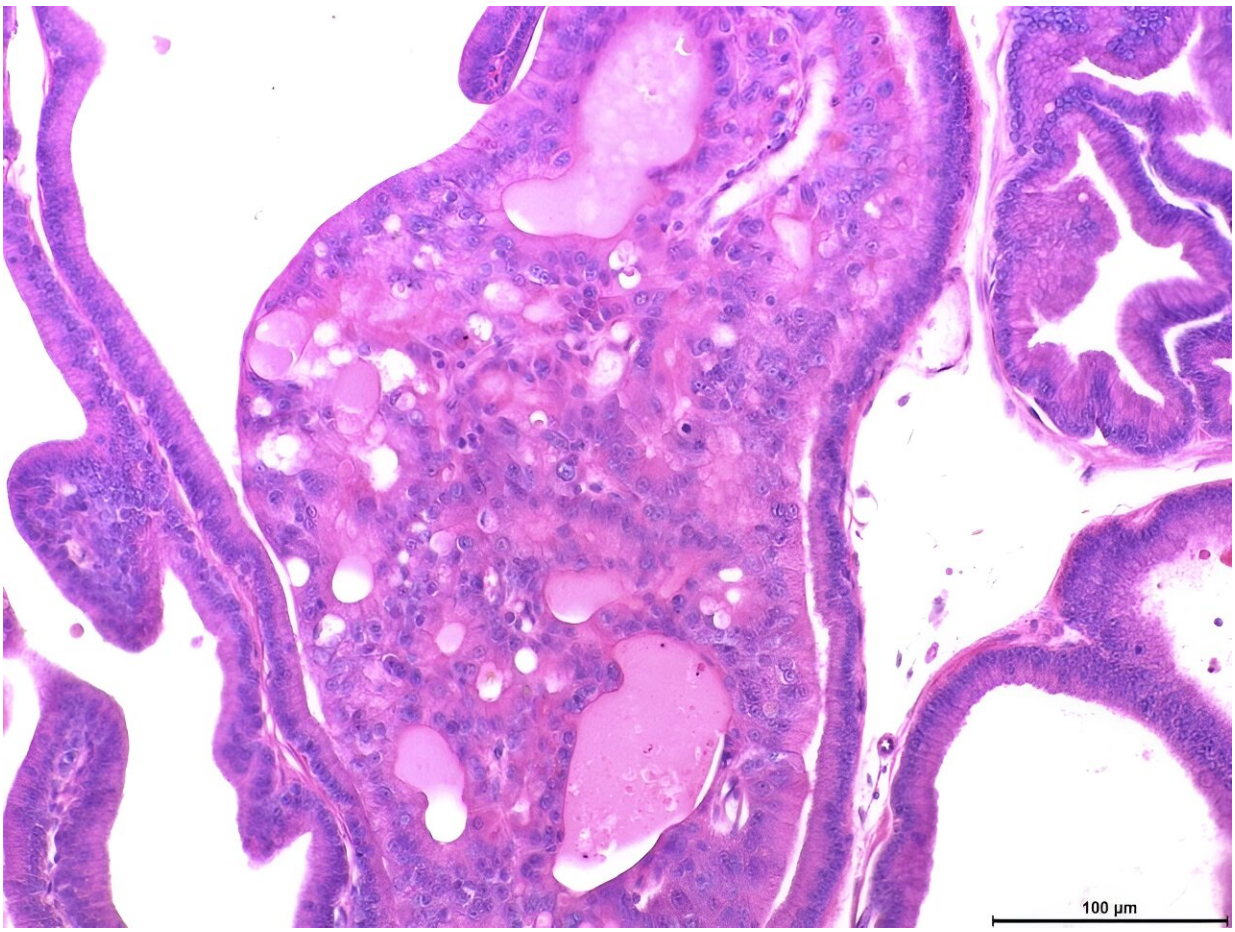
Research explains why protein-poor diet during pregnancy increases risk of prostate cancer in offspring

January 24 2024, by Maria Fernanda Ziegler



Prostate cancer cells in rats submitted to maternal protein restriction. Credit: FAPESP

Experiments with rats conducted by researchers at São Paulo State University (UNESP) in Brazil increase our understanding of why descendants of women who were malnourished during pregnancy tend to face a higher risk of prostate cancer in adulthood.

In a first study appearing in *Scientific Reports*, the researchers detected alterations in gene expression that may have been associated with the hormone imbalance observed in the rats' offspring and the heightened risk of prostate cancer.

"Lack of protein during gestation and lactation deregulates the molecular pathways involved in normal development of the prostate, leading to impairment of its growth in young offspring. This was already known. We've now discovered that a protein-poor diet during the embryo stage and the first two years after birth alters the expression of more than 700 genes in offspring, including the gene ABCG1, which is associated with prostate cancer," said Luis Antônio Justulin Junior, who leads the research and is a professor at the Botucatu Institute of Biosciences (IBB-UNESP).

In a second study published in *Molecular and Cellular Endocrinology*, deregulation of a specific type of RNA (microRNA-206) correlated with an early-life increase in the hormone estrogen, a pronounced trait in the offspring of female rats fed a protein-restricted diet during gestation and lactation, and a factor associated with a heightened risk of prostate cancer.

"The results showed once again how much diet and everything else that happens in the initial stages of development determine the trajectory of health and disease in offspring. They were a key contribution to our understanding of the first 1,000 days of life, the period comprising pregnancy, breastfeeding and infancy until the baby's second birthday," Justulin said.

Lifelong influence

Research into the links between maternal health and the development of offspring has advanced significantly in recent decades, especially in a field known as developmental origins of health and disease (DOHaD). There is ample evidence that inadequate gene-environment interaction during the embryo stage and the first two years after birth can be a key factor in increasing the lifelong risk of non-communicable chronic diseases (NCCDs), such as cancer, diabetes, chronic respiratory disorders and cardiovascular disease.

According to an international study reported in 2009, the risk of prostate cancer was well above normal in Jewish men exposed in early childhood to starvation and the horrors of the Holocaust. The study of how behavioral and environmental factors such as maternal malnutrition affect gene expression is called epigenetics. Epigenetic changes are reversible and do not change DNA sequences by causing mutations. They can change how the organism reads a DNA sequence and alter the expression of genes in offspring. New patterns of gene expression can be transmitted to future generations.

The research pursued at UNESP investigated the cellular mechanisms involved in this process by means of experiments with rats. Some of the results are presented in the article published in *Scientific Reports*. The authors describe the global expression profile of microRNA and messenger RNA, highlighting the molecular alterations associated with a heightened risk of prostate cancer. It is worth recalling that microRNA modulates expression of messenger RNA via epigenetic mechanisms, and that messenger RNA plays a crucial role in protein synthesis. Thus, microRNAs are important factors in gene expression.

Having produced RNA sequences and analyzed them using bioinformatics, the researchers concluded that prostate cancer in

maternally malnourished offspring and older rats exposed to intrauterine protein restriction could be due to early-life deregulation of miR-206 and its target gene PLG, and that this deregulation was likely to be a response to abnormally high levels of estrogen during pregnancy.

"We also found that miR-206 modulates expression of the estrogen receptor alpha (ERα), which is believed to be associated with the increased risk of prostate cancer in adulthood," Justulin said.

Hormone imbalance was observed in early life, in addition to differences in glandular development and growth, he explained. "These animals had higher levels of estrogen, which rose even more as they aged, while androgen levels fell. This hormone imbalance is associated with the development of prostate cancer in humans," he said.

The article published in *Scientific Reports* was awarded a prize at the first DOHaD conference held in Brazil by Associação DOHaD Brasil.

Target gene

In the article published in *Molecular and Cellular Endocrinology*, the group described alterations in more than 700 genes in the prostates of rat offspring, identified by RNA sequencing (RNA-seq), which measures the expression of several genes to obtain the transcriptome, the complete set of RNA molecules present in the cells of a tissue sample.

When the researchers looked for correlations between the results of the study and a human prostate cancer database, they found that ABCG1, one of the altered genes, was a potential "DOHaD gene" associated with disturbances in prostate development, which have lasting effects that could heighten the risk of cancer.

"We showed that changes in the gene expression profile can persist

throughout the lives of rats, predisposing them to prostate cancer as they age. Curiously, we identified molecular markers that are frequently deregulated in both young and old maternally malnourished offspring rats, as well human prostate cancer patients. The data pointed to maternal malnutrition as a key environmental factor in the origin of prostate cancer in rat offspring," Justulin said.

More information: Luiz M. F. Portela et al, Early-life origin of prostate cancer through deregulation of miR-206 networks in maternally malnourished offspring rats, *Scientific Reports* (2023). DOI: 10.1038/s41598-023-46068-1

Ana CL. Camargo et al, Deregulation of ABCG1 early in life contributes to prostate carcinogenesis in maternally malnourished offspring rats, *Molecular and Cellular Endocrinology* (2023). DOI: 10.1016/j.mce.2023.112102

Provided by FAPESP