Revealing the Secrets of the Ovary

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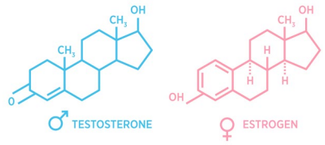
REVEALING THE SECRETS OF THE OVARY

Professor JoAnne S. Richards conducts her vital research at the Baylor College of Medicine in Houston, Texas, in the USA. For decades she has investigated how certain hormones regulate ovarian function at particular stages of the menstrual cycle, as well as developing new ways to study ovarian cancer. Her work also helps shed new light on common female reproductive health disorders that can affect fertility.



A Delicate Balance of Hormones

The human menstrual cycle takes about 28 days, during which the lining of the womb (uterus) grows thicker in preparation for pregnancy, whilst the ovaries undergo changes to produce a mature egg/oocyte. If a pregnancy does not occur, then the uterine lining is shed, and menstruation occurs. Each ovary contains thousands of primordial and small growing follicles, each of which contains an immature egg, one that has not yet fully matured. At mid-cycle, when a preovulatory follicle develops, and the enclosed egg has matured, the egg surrounded by specialised cumulus cells is then released and attached to the surface of the ovary, where it can be collected by the fallopian tube (also known as an oviduct) where it could potentially be fertilised by sperm (if there is any present).

Several hormones work in a delicate balance to achieve ovulation every month, with each hormone having its own particular role. Follicle-stimulating hormone (FSH) causes small follicles and the contained egg in the ovary to mature, whilst luteinising hormone (LH) triggers ovulation, the release of a mature egg. Oestrogen and progesterone help maintain the uterine lining for implantation and pregnancy; they also regulate pituitary function to control the release of FSH and LH.

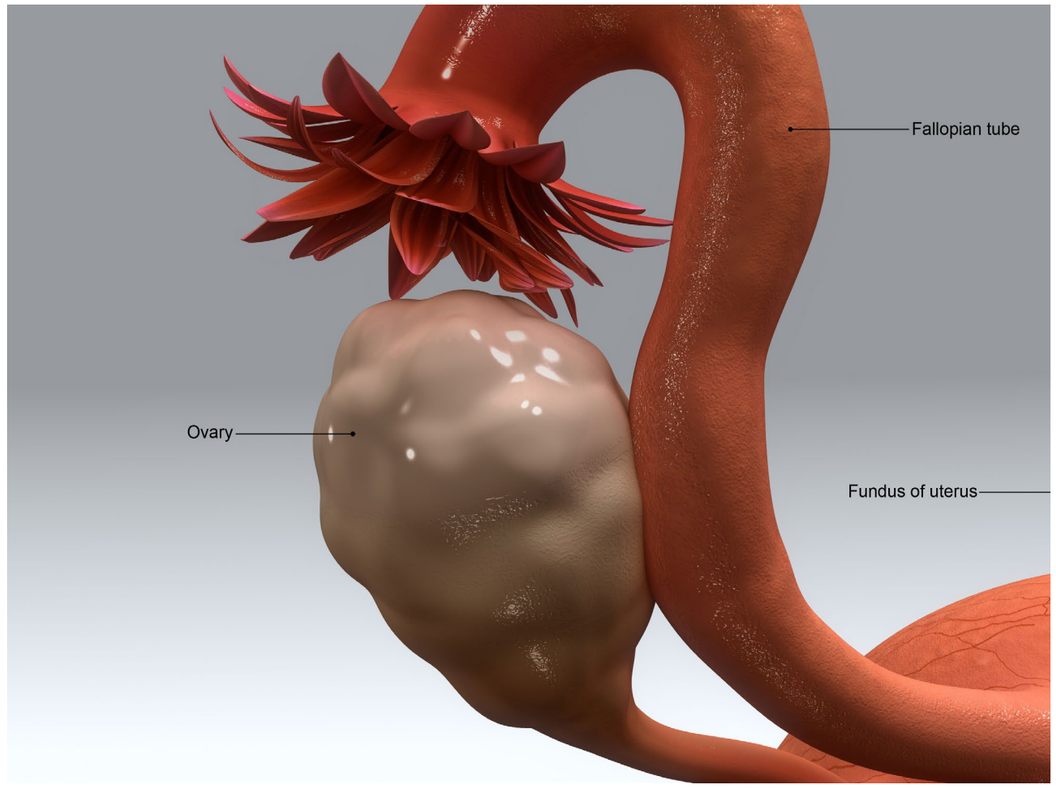
Professor JoAnne S. Richards works at Baylor College of Medicine, a leading centre for molecular biology and gene cloning science. Her decades of research have advanced our understanding of the molecular and cellular mechanisms that control ovulation, ovarian follicular development, and, importantly, ovarian cancer. According to the Centres for Disease Control and Prevention in the USA, ovarian cancer is the second most common gynaecological cancer in the USA and causes more deaths than any other cancer of the female reproductive system. Professor Richard's work not only opens up new avenues for potential therapies for this disease but also other female reproductive health conditions, like polycystic ovary syndrome (PCOS) and premature ovarian failure, which can affect fertility as well as cause a myriad of unpleasant symptoms.

The Mutant Mouse

Professor Richard's early research highlighted that there is a lot more happening during ovarian follicular development than was first thought. It's not a simple case of FSH stimulating follicle growth and the egg suddenly maturing – there are many intricate steps involved. She has reviewed studies that indicate other signalling cascades occurring within the ovary itself that can affect follicular development, as well as how the various hormones interact at the different stages of follicular development and ovulation.

Signalling cascades (pathways) are complex, multi-step processes that occur within cells in which a group of molecules, such as proteins and enzymes, work together to control a particular outcome, in this case, the development of the follicle. These cascades start when a signal, like a hormone from the environment, reaches the cell, binding to a specific receptor on the cell surface or within the cell. They also cause specific genes to be turned on or off in order to control the production of various protein molecules involved in specific pathways.

Mutant mouse models (transgenic mice) allow the study of particular genes.



Transgenic mice are genetically modified and are commonly used to help understand the role of certain genes in animal models of diseases or conditions found in humans. Looking at mutant mouse models coupled with clinical evidence, Professor Richards identified some of the most powerful regulators of follicular development within the ovary, being the RAS/ERK1/2 signalling pathways and the FOXO1/FOXL2 transcription factors.

Professor Richards and her team also developed novel mouse models of the granulosa cell (follicular cell) and ovarian surface epithelial (OSE) cancer – the 'OSE mutant mouse'. Using the OSE mutant mouse allowed for a better understanding of this disease, paving the way for new therapies. Her work also resulted in the identification of genes and signalling pathways that regulate certain stages of ovarian follicular development and ovulation, specifically the roles of ADAMTS1, TNFAIP6 and PTGS2.

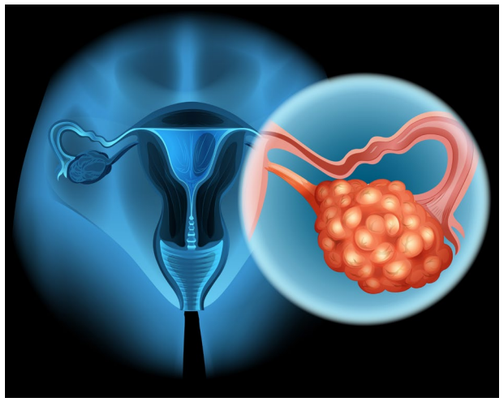
Investigating Polycystic Ovary Syndrome

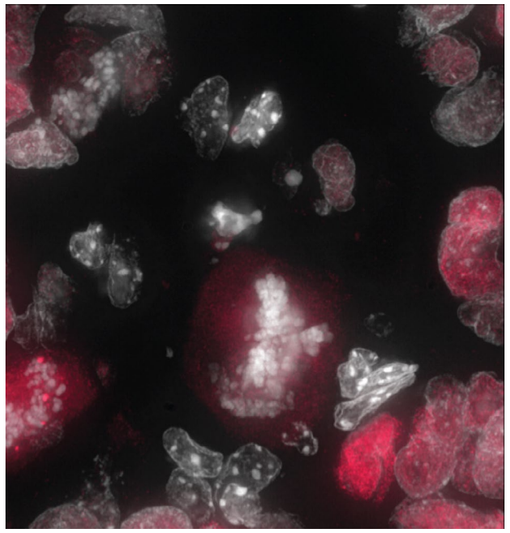
PCOS is a very common condition which affects how the ovaries work. It is thought to affect as many as 1 in 10 women, although not all show symptoms. Sufferers can experience difficulty getting pregnant, irregular periods, excessive hair growth in unwanted places but hair thinning or loss on the head, as well as weight gain. It's also associated with an increased risk of type 2 diabetes in later life. Ovaries are enlarged with many fluid-filled follicles (not cysts as implied by the name of the condition), and often the eggs are underdeveloped, and the follicles do not release them because ovulation fails to occur. Sufferers are characterised by producing an excess of ovarian theca cell-derived androgens, or 'male' hormones.

In 2016, Professor Richards and her team investigated this condition which is also linked to systemic low-level inflammation. They carried out gene profiling and examined granulosa-lutein cells from women undergoing in vitro fertilisation, a process to help women who are having fertility problems conceive. They studied women both with and without PCOS and also compared cytokines and other inflammatory markers. Professor Richards concluded that within the follicles, androgens and cytokines create a regulatory loop that affects how the granulosa-lutein cells in the follicles produce other cytokines and chemokines (molecules that usually attract white blood cells of the immune system to infection sites). Professor Richards concluded that androgen excess is a major contributor to PCOS and went on to further explore this condition.

Exploring the Role of Theca Cells

The following year, Professor Richards reviewed studies pertaining to follicular development in PCOS and also





Polyploid giant cancer cell. Credit JoAnne Richards.

premature ovarian failure to present a comprehensive summary of the findings. She focused on theca cells, which have a diverse number of roles during the formation of follicles, from synthesising androgens and vital growth factors to providing structural support and protection for the growing follicle. In particular, she reviewed the mutant mouse models used to investigate various signalling pathways and a variety of factors that impact theca cell development and function. She integrated all the current data from both PCOS and non-PCOS sufferers to understand what pathways and factors contribute to follicle growth as well as to the abnormal function of theca cells.

Since ovarian theca cells have such a critical role in follicular development but also have a role to play in the dysfunction of the ovaries in PCOS, premature ovarian failure and other conditions such as ovarian hyperthecosis, Professor Richards stepped up to advance the research into theca cells. She already knew that theca cell androgen production in the ovaries is regulated by LH and various factors within the follicle. She argued that the enhanced production of androgens by the theca cells contributes to PCOS. However, she noted that the consequences of high levels of androgen in the ovaries remained poorly understood.

In 2019, Professor Richards carried out a ground-breaking study documenting the molecular events that are changed in the theca and stromal (structural support) cells of mice that are exposed to high levels of androgens, using a non-metabolisable form of testosterone, called dihydrotestosterone (DHT) that cannot be converted to estrogens. She found changes in ovarian morphology (structure and form) as well as function within the follicles and also the areas outside. In the study, after treating female mice with DHT for a set time, Professor Richards analysed the activity or expression of particular genes and, in turn, the production of various proteins and other molecules involved in cell signalling pathways.

In particular, she found increased specific expression of VCAM1 (vascular cell adhesion molecule 1) in the theca cells (and not the granulosa cells, which many previous studies focused on) of developing follicles of the DHT-treated mice. These findings indicated new functions of VCAM1 in the reproductive organs, deepening our understanding of how high levels of androgens impact ovarian functions.

A New Hope for Tackling Ovarian Cancer

The American Cancer Society estimates that close to 20,000 women will be diagnosed with ovarian cancer in 2023 in the USA, with about 13,000 dying as a result. Professor Richards and her team have documented that the disruption of particular genes and signalling pathways, FOXO1, FOXO3 and PTEN, of granulosa cells in the ovaries leads to the formation of tumours. Using their unique OSE mutant mouse model, Professor Richards and her team have shown that the genetically altered, or mutant status, of a particular tumour protein, p53, changes the way the tumour responds to hormones. They are using their model to further investigate the p53 alleles (parts of genes) in human ovarian cancer growth and response to hormones.

Professor Richards is also exploring potential new avenues for treatments. She states that the first-line treatment for patients with a certain form of ovarian cancer, high-grade serous ovarian cancer (HGSOC), involves using cytotoxic drugs. However, tumours frequently recur and with increased resistance to the drugs used to treat them, resulting in poor survival rates. She is examining data surrounding particular markers of cell division and polyploidy giant cancer cells (PGCC), a type of cell found in HGSOC which appear to play a key role in producing more drug-resistant cells, thereby assisting the progression of the tumour. She argues that developing drugs to target PGCC could be a new approach to reducing the occurrence of drug-resistant tumours, bringing new hopes for tackling this devastating disease.

Meet the researcher

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Professor JoAnne S. Richards has had a long and decorated career. Over the years, she has made many significant contributions to the field of reproductive biology, including developing a novel animal model to enable the study of ovarian cancer, identifying new pathways that regulate ovulation and the role of androgens in theca cells, as well as discovering a new cyclooxygenase gene. Professor Richards achieved an AB in Biology in 1967 at Oberlin College, Ohio, and went on to study at Brown University in 1968, where she received an MA in Arts and Teaching. In 1970, she completed her PhD in Physiological Chemistry at Brown University, and in 1973, she received a postdoctoral position in Reproductive Endocrinology at the University of Michigan. Her academic progression included positions at the University of North Dakota and the University of Michigan before being appointed Associate Professor at Baylor College of Medicine in 1981 and then Professor in 1988, where she remains to this day.

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KEY COLLABORATORS

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Baylor College of Medicine

FUNDING

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