The influence of female hormones on immunity

Regulated Resistance

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How can a properly functioning female immune system be reconciled with the events of fertilization and reproduction? Male sperm is foreign, after all, and should be destroyed by the female body. Female mammals cope with this dilemma through the cyclical influence of sex hormones on their immunity

One of the most characteristic traits of the placental mammals is the structure and function of their reproductive system. Mammals also possess a highly specialized immune system, precisely distinguishing between the body's own structures and potentially dangerous pathogens. That gives rise to a problem which first attracted attention back in the early 19th century: for the female immune system, male sperm is foreign and should be destroyed. Embryonic cells, too, should trigger an immune reaction aimed at their elimination. Fortunately, evolution worked out a compromise that enables females to reconcile their own immune activity with their reproductive functions.

The sex cycle, consisting of two stages, occurs in all healthy, adult females of a given species. In the first stage, an oocyte ready for fertilization is produced and released into the reproductive tract. The cells forming the uterine mucous membranes undergo intense cell division to enable the future embryo to implant itself. In the second stage of the cycle, mucous membrane cells curb their division to form optimal conditions for the embryo's development.

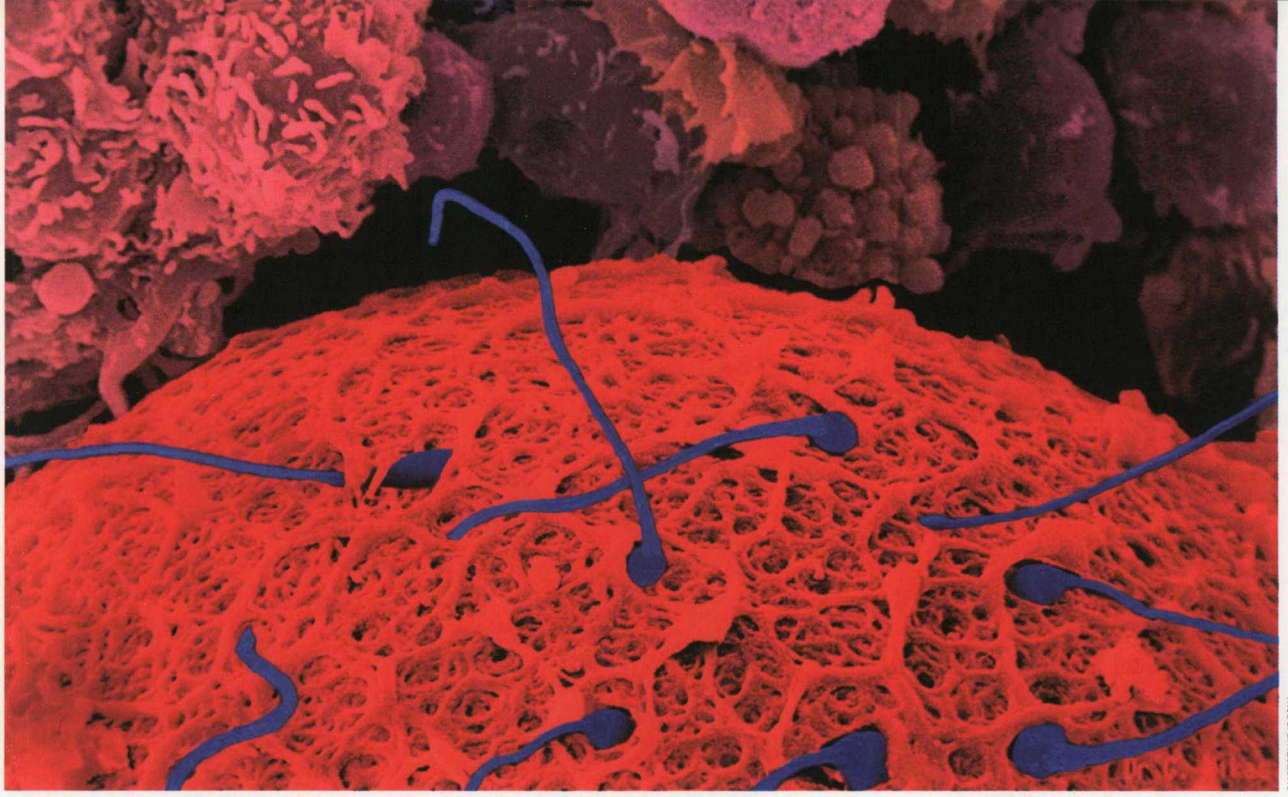
Immunity comes full circle

Cyclical changes in the reproductive system are regulated by the central nervous system, which influences the pituitary gland by releasing neuropeptides from the hypothalamus. The pituitary, in turn, releases hormones which directly regulate the function of the ovaries (follicle-stimulating hormone - FSH and luteinizing hormone - LH). Cyclical changes in sex hormone concentrations meant to regulate the reproductive system also have an impact on the function of the entire organism. Immune system cells, or leukocytes, constantly circulate through the body. After leaving the blood vessels many of them remain in various tissues and participate not only in processes that destroy pathogenic factors, but also in rebuilding tissues, thus contributing to maintaining homeostasis. Leukocytes are influenced by factors that selectively target a given organ, which therefore includes the sex hormones. Changes in uterine mucous membranes during the sex cycle are in part related to changes in their leukocyte content. More leukocytes are present in the vagina, intercepting and eliminating infectious factors even before they can reach the uterus. When there is a high concentration of estrogens - i.e. during the first stage of the cycle, prior to ovulation - the number of immune cells is higher in both the vagina and uterus. When the concentration of progesterone rises, in turn, the number of leukocytes in the reproductive tract drops. This happens, therefore, at precisely the same time when sperm, and later an embryo, may be expected to be present. The sex hormones determine the strength of the anti-infectious response, and their mutual concentrations play a significant role in how a given pathogen is fought. A good example of the sex cycle's impact on immune reactions can be found in the progression of *Chlamydia trachomatis* bacteria infections: when there is a high concentration of progesterone and a low concentration of estrogens, an intrauterine infection triggers a strong immune reaction, but in the reverse situation the bacteria are fought only weakly.

Hormones regulate the activity of the immune cells. The number of leukocytes in the female reproductive tract and their composition fluctuate over the sex cycle.

Cyclical changes in sex hormone concentrations affect the function of the entire organism

A key role in recognizing foreign antigens is played by macrophages and antigen-presenting dendritic cells. These are cells which cooperate closely with T lymphocytes, communicating information about the chemical structure of foreign bodies. As it turns out, the number of antigen-presenting cells in the vagina is not high during ovulation, but increases during the second stage of the cycle. That means that the presence of sperm in the vagina is not greatly noticed during oestrus (when a female is in heat). The occurrence of dendritic cells in the uterine mucous membranes and spleen of mice is highest during ovulation,



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but their frequency wanes in tandem with the concentration of progesterone. When oestrus is over, i.e. when any sperm have already reached the uterus and oviducts, the vagina regains its immunological reactivity and can react fully to the presence of infectious factors. Changes in the frequency of lymphocytes in the uterus seem to be dictated by the possible presence of an embryo or fetus.

Molecular underpinnings

Immune reactions may proceed locally or systemically, occurring in the peripheral lymphatic organs. The cyclical rhythm of sex hormone action affects immune processes in general. The activity of the immune system is different in females in the first phase of the cycle than in males or in females in the second phase. In the first phase, the immune system cells in the spleen increase their capacity for division and the composition of secreted cytokines changes. Female mice then stand greater chances of surviving sepsis. The administration of estrogens usually serves to boost the immune system. But a high level of progesterone significantly more frequently has an unfavorable impact on the course of an infection (for example involving the HSV-2 virus, *C. trachomatis*, or *Listeria monocytogenes*).

The cyclical interactions between the endocrine and immunological systems have molecular underpinnings. The basic question is: By what mechanism do hormones influence the leukocytes? All hormones act by means of receptor proteins. After entering a cell, a hormone binds to the proper receptor, which in turn binds to specific DNA locations and activates the target genes. Leukocytes possess receptors for the sex hormones, which may be involved in regulating their cell functions. These mainly include two types of receptors for the estrogens ERalpha and ERbeta, as well as two for progesterone PRA and PRB. Research on the impact of the sex hormones on immunity indicates that ERalpha estrogen receptors are of fundamental significance for many phenomena. They seem to be related to women's higher rate of contracting autoimmune diseases as well as to changes in immunity seen after a hemorrhagic shock.

ERalpha and phase of the cycle

Aware that immune system cells contain ERalpha and are subject to regulation by the sex hormones, we posed the following question: Are fluctuations in ERalpha production during the course of the sex cycle observable in cells with high capacity to regulate the immune response? We tested levels of ERalpha in macrophages in the uterus (tissue directly regulated by the sex hormones) and in the spleen (lymphatic tissue not directly linked to the reproductive system). ERalpha levels turned out to fluctuate based on the sex cycle phase in the macrophages of both organs – being lower prior to ovulation, when estrogens are dominant, than during the second half of the cycle. After fertilization these levels clearly increase in the macrophages of the spleen, but remain unchanged in the uterus. We do not know whether lowered ERalpha levels when sperm could be located in the female reproductive tract is one of the mechanisms that fosters immune tolerance of the antigens of the male gametes. It is also unclear how ER fluctuations in the immune system cells underlies the observed changes in female immunity. We can say with certainty, however, that cyclical changes in ER levels serve as a sensitive gauge of direct hormone impact on immune system cells. ■

Further reading:

Hughes G.C., Clark E.A. (2007). Regulation of dendritic cells by female sex steroids: relevance to immunity and autoimmunity. *Autoimmunity, 40*, 470–81.

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