INFLAMMATION

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PYKNOTIC

CASE 1: Recurrent COVID infection

A 57 yo WF yoga instructor canceled her Monday class because of mild fever, weakness, and a positive at home test for the COVID virus.

Question 1: What further information would you ask of the patient

Question 2: What is the expected course of this illness

Question 3: What is the expected viral load and antibody levels over next 10 days

Question 4: How does exposure to antigen (vaccine or virus) cause the body to produce antibodies

Case 2: In August, I experienced both marked arm swelling due to a bee sting, and a local rash due to poison ivy

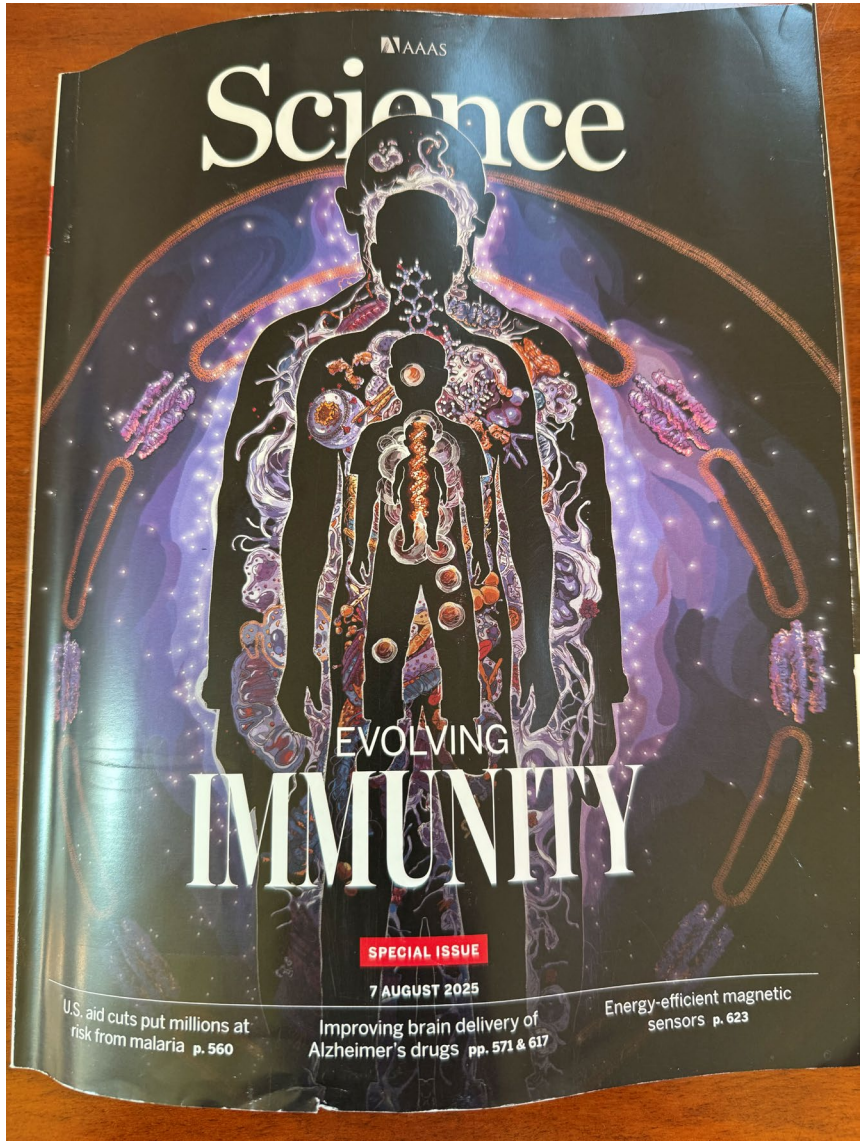
Question 1: Despite experiencing bee stings several times a year (I keep bees to produce honey), I have never before before had a reaction. What happened this time

Question 2: What is the time course of immune reaction after a bee sting, ie Immediate Hypersensitivity

Question 3: What treatment did I take for the bee sting
ice, diphenhydramine (Benadryl), ? Epinephrine injection

Question 4: What is the time course of the skin reaction to poison ivy, ie Delayed Hypersensitivity

Question 5: What treatment did I take for the poison ivy, topical cortisone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SPECIAL ISSUE

THE MULTIFUNCTIONAL IMMUNE SYSTEM

SARAH ROSS and CAROLINE ASH

The survival of single-celled and multicellular life requires immunity to pathogens. In humans, immune defenses are multilayered, combining molecules that sense and signal the presence of threats with a range of specialized cells that patrol the body. Although surveillance and defense are central to the purpose of the immune system, additional physiological roles have emerged alongside them.

This Special Issue explores the immune system at the molecular and cellular levels and how it has evolved to govern multiple facets of human health. Over millennia, pathogens have exerted evolutionary pressures that have diversified molecular defense mechanisms. Innate and adaptive immune cells cause damage as they eliminate infection, and the immune system itself can help to repair tissue. We now appreciate that some immune cells can reside within tissues, with their specialized roles in defense being harnessed to promote organ function in the absence of infection. Immune cells are influenced by reproductive biology, too, with immune cell networks exhibiting differences between females and males. These functionalities were established through the selection of beneficial genetic traits over countless generations. Yet the immune system also changes within a single human lifetime, from birth to adulthood and through older age, shaped by the environment, microbiomes, and the process of aging.

As we understand more about the integral role of the immune system in responding to pathogens and its broader role in tissue function, we must evolve how we think about its contribution to human health. Interdisciplinary research, which incorporates molecular and cellular immunology into the function of other physiological systems, is critical as we seek to advance therapeutics and achieve personalized health care. 10.1126/science.aea8294

ILLUSTRATION: RIOKA HAYAMA

I. Complexity of the INFLAMMATORY SYSTEM

input (sees Ag's, neural connections). Antigens. Molecules that provoke the immune system

output (produces humoral and cellular Ab's; cytokines)

Antibodies. Protein molecules, free or attached to cells that are produced in response to Ag

Cytokines. Protein molecules that modulate the immune system and general response of the body

Cellular response of the immune system: neutrophils, B and T lymphocytes

memory (remembers past experiences, innate knowledge)

Antibodies and memory lymphocytes

distributed processing (modulates responses based on all of the above)

bone marrow, lymph nodes, GI tract,

connections to brain, gut, skin

ns are likely a con-
mmune networks.
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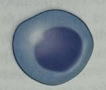
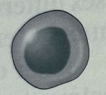
Adaptive immune system

B cells
- Respond to estradiol (E2), androgens, response to progesterone unknown/not responsive
- Broader and more effective antibody response in females
- Comparable numbers and activity in males and females



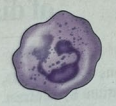
Conventional Cd4 T cells
- Respond to estradiol (E2), progesterone, and androgens
- Higher numbers and activation in females; higher CD4/CD8 ratio in females

Cd8 T cells
- Respond to estradiol (E2), progesterone, and androgens
- Males trend toward exhaustion, females trend towards activation
- Higher numbers and activation in females

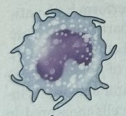


T_{reg} cells
- Respond to estradiol (E2), progesterone, and androgens
- Higher numbers and more robust responses in males

Innate immune system

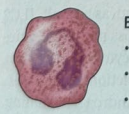


Neutrophils
- Respond to estradiol (E2), progesterone, and androgens
- Female sex hormones promote longevity and effector functions
- Higher numbers and phagocytic activity in females

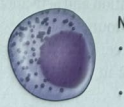


Monocytes and macrophages
- Respond to estradiol (E2), progesterone, and androgens
- Greater activation and phagocytic activity in females
- Higher proinflammatory cytokine production in males

Dendritic cells
- Respond to estradiol (E2), progesterone, and androgens
- Higher pDC responses in females activating T cells
- Sex-specific number variations in some tissues



Eosinophils
- Respond to estradiol (E2), progesterone, and androgens
- Male dominance in eosinophilic diseases
- Higher blood counts in males but variable tissue responses



Nk cells
- Respond to estradiol (E2), progesterone, and androgens unknown or not responsive
- Sex and tissue-specific variations in numbers and activity

Fig. 2. Characteristics of human immune cells and their responsiveness to sex

knockout of ERα in female mice resul
cells that display the phenotype of m
diet–fed obese mice, ST2+ VAT T_{reg}
increase in female mice with no cha
mized female mice, suggesting a ro
female mice from obesity-induced

Balancing homeostasis with pro
act, and if dysregulated, autoim
general, males exhibit higher rate
productive cancers compared wit
both sex and environmental fact
is a distinct immunological niche
pro- and antitumor immune cells
hormone signaling is important
treatment efficacy in preclinical
has been demonstrated to promo
cells (43) and the depletion of an
androgen signaling promotes th
to terminally exhausted CD8+
signaling–based male bias in the
cells, which are implicated in re
point blockade (46), perhaps e
to this therapy.

Developmental differences a tissue immunology

Sex-based differences in immun
tal processes that shape tissue
lungs, sex-based differences in
are observed as early as 16 to
adulthood (47). Prepubescent
severity of asthma compared v
among adults, asthma afflicts
introduces a range of sex-spec
ing, shifts in sex hormone lev
are implicated in adult asthm

The brain is also a develop
brain tissue or region size an
cell types express sex horm
effects on innate immune r
brain (49). Microglia from
male mice have distinct tra
independent of estrogen (4
transplanted into microglia
tained a female-specific ex
females 5 days after transp
etic basis of sex differences
artery occlusion in mice re
48 hours. Transfer of femal
microglia into female bra
(49). Lipopolysaccharide-t
mice also have sexually di
developmental differences
both genetics and sex horm
of microglia and brain de

IV. IMMEDIATE HYPERSENSITIVITY. bee sting

BEE STING

1-3 uL of venom, toxic local damage, then presentation of foreign Ag

IgE antibody + eosinophil response

small local swelling to anaphylactic shock and death

Do you have to have been exposed to a bee sting once before in order for an antibody to exist? (YES)

Will the reaction always bee the same, ie serious bee allergy

Rx. Epipen

PEANUT BUTTER

Ag in peanuts is exposed via columnar epithelium in the GI tract

V. DELAYED HYPERSENSITIVITY. poison ivy

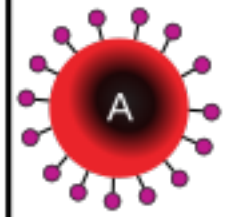
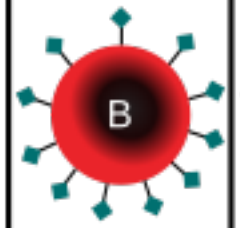
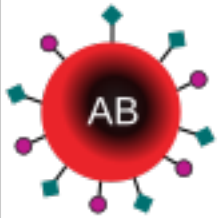
Allergen is urishol oil on plant

Antigen is presented by cutaneous dendritic cells

activated Help T cells from previous exposure, respond

Rx. anti itching OTC. or topical steroids

? Can an HIV patient with a very low Helper T cell count respond to poison ivy?

	Group A	Group B	Group AB	Group O
Red blood cell type				
Antibodies in plasma	 Anti-B	 Anti-A	None	 Anti-A and Anti-B
Antigens in red blood cell	 A antigen	 B antigen	 A and B antigens	None

Autoantibodies exist before any know exposure to antibody

Why do Red Blood Cell Group Surface Ag’s Exist?

VI. AUTOIMMUNE DISEASE. Rheumatoid arthritis

Although the exact cause of RA is unknown, initiation of disease seems to result from an interaction among genetic susceptibility, environmental triggers, and chance.

smoking, female, certain HLA-DR subtypes, infection with many agents

Major Histocompatibility Complex. (MHC)

why do we have auto antibodies against everyone else