Katherine Gundling, MD

BIOGRAPHY:

Katherine Gundling, MD, is Associate Clinical Professor of Allergy and Immunology at UCSF, and Practice Chief of the Allergy/Immunology clinic at Moffitt Hospital. After undergraduate studies at Stanford University, she worked for several years in the medico-legal arena and for Linus Pauling before completing premedical requirements, and attending medical school at the University of Rochester. She was Director of Medical Education for the department of Internal Medicine at UC Davis for 8 years, and is the recipient of numerous teaching awards for her work with students and residents. In 2009 she completed editing, “The ACP Guide to Evidence Based Complementary and Alternative Medicine,” and she has performed a clinical trial of immunomodulatory properties of *Panax ginseng*. Currently she is also building the Allergy/Immunology curriculum for the UCSF community, and investigating the genetic underpinnings of common variable immunodeficiency.
Immunology 201: Application of the Basic Concepts to People

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Summary of what we have learned so far

- Immunology 101: The Basics and Introduction to our Patient
- Pharmacology: Bugs and Drugs, Part 1
- Pharmacology: Bugs and Drugs, Part 2
- Genes, Genomes and Human Disease, Part 1
- Genes, Genomes and Human Disease, Part 2
- Immunology 201: Application of the Basic Concepts to People

Immunology 101: The Basics and Introduction to our Patient

- The immune system works on our behalf every moment of our lives
- It defends us against external and internal causes of disease
- Major cells of the immune system start in the bone marrow, move to virtually all areas of the body, and participate in a vast communication network
- The ability of the immune system to work properly is affected by genetic and environmental influences

The Lymphatic System
Major sites of immune activity

Development of Cells

Sentinel cells in tissues
Examples: macrophages, dendritic cells, mast cells

Circulating cells
Examples: neutrophils, monocytes, eosinophils, lymphocytes

Tissue cells
Examples: epithelial cells (structural)
General time course of the immune response to infection

**Innate immunity:** 0-4 hours
- Recognition; response by preformed, non-specific mechanisms

**Early induced response:** 4-96 hours
- More precise recognition of microbes
- Recruitment of inflammatory response

**Adaptive immune response:** >96 hours
- Transport to lymphoid tissue
- Specific identification of microbe
- B and T lymphocytes respond with directed antibodies or effector cells

Adapted from Janeway

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**Innate Immunity Summary (1)**

- Mechanical/Physical barriers
- Chemical barriers and antimicrobial peptides
- Microbiological competition
- Complement system
  - Plasma proteins that “tag” bacteria for destruction
- Toll Like Receptors (recognize general features of the enemy)

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**Innate Immunity Summary (2)**

Phagocytes – ingest harmful, foreign particles, and dead or dying cells

**Phagocytosis**
“to devour” “cell” “process of”

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**Antigen**
A substance either within or outside the body that triggers the immune system to produce antibodies against it

**Antibody**
A protein (immunoglobulin) produced by B cells (lymphocytes) in response to specific triggers by “foreign” substances. They identify and neutralize their target
T cell-B cell interaction video

Lymphocytes
After identification of the invaders, lymphocytes generate an immunologic response that specifically and maximally targets that pathogen.

They also generate “memory” cells for future protection.

It’s easy to kill bacteria, viruses, and other invading organisms...

...but it is hard not to kill the host along with them!

We must create antimicrobial, antiviral and antifungal drugs that specifically target the differences between “us” (humans) and “them” (microbes).

Bugs and Drugs
Dr. Kruidering-Hall

Key Concepts
Overview of Drug Targets

1. Inhibition of cell wall synthesis
   - Penicillins, cephalosporins, vancomycin
2. Inhibition of protein synthesis
   - Aminoglycosides, macrolides, tetracycline
3. Inhibition of nucleic acid synthesis
   - Antiviral agents, fluoroquinolones
4. Inhibition of folic acid synthesis
   - Sulfonamides, trimethoprim
5. Disruption of cell membrane function
   - Antifungal agents

Also discussed the concepts of drug resistance and the need for all of us to play an active role in its prevention and delay

What are examples of our actions that lead to antibiotic resistance?

The ABC’s of Genes and Genomes

DNA = “letters”

Genes = “words”

Chromosomes = “chapters”

Genome = Entire book ~
A manual for creating a living being!!
Alleles

- **Wildtype**
- **Mutation 1**
- **Mutation 2**

**Homozygous**
- Wildtype
- Mutant

**Heterozygous**
- Compound

**Consequences of Genetic Variation Vary**

- **Rare, high impact on health**
- **Common, low impact on health**

“**Mutations**”

- **Genetic Disease** (e.g. cystic fibrosis, Tay Sachs disease)
- **Benign phenotypic differences** (e.g. hair/skin color, asparagus smell)
- **Neutral Variants**

**Frequency of variant in population**

- **1%**

**Spectrum of Genetic and Environmental factors that lead to disease**

- **Genetic**
  - Cystic fibrosis, Down syndrome
  - CVID

- **Multifactorial**
  - Diabetes, stroke, hypertension, Alzheimer dz
  - CVID

- **Environmental**
  - Diet, lifestyle, etc.
  - Measles, lung cancer

**Genetic Testing**

- Single gene
- Chromosome
- Whole genome

**Returning to Elizabeth...**

- **Primary immune deficiency**
  - Common variable immunodeficiency (CVID)
- She does not make antibodies, and is therefore susceptible to infections (mostly predictable).
- In the right situation antibiotics can greatly reduce “morbidity” and “mortality” for patients with CVID.

She HAS been admitted to Nursing School!

**What does your patient really want to know?**

Doctor, what is going to happen to me??

Hmmm.....

In medical terms, the patient is asking, “Doctor, what is my prognosis? Can you predict my clinical PHENOTYPE?”

**PHENOTYPE =**

Sum total of: Genotype + Environment + the way genes and environment interact
Example of the Importance of Environment:
Two patients with exactly the same “CVID genes” (theoretically speaking)
One is an inner city preschool teacher...
The other lives alone in the Nevada desert...

How might their “phenotypes” differ?

Example of the Importance of Genetics:
Two patients in identical environments (theoretically speaking)
One has a defect limited to B cells and the production of antibodies
The other has a defect of T cells, leading to the same defect of B cells and antibody production, BUT ALSO T cell abnormalities of immune dysregulation

How might their phenotypes differ?

Spectrum of CVID associated health challenges
Increased incidence of:
Autoimmune diseases
Several different types of cancer
Inflammatory lung diseases
Enlarged spleen
Viral infections

But at least 25% have no complications!

Why might genetic analysis be helpful for people who have CVID?
Is there a strong correlation between the genetic profile and the long term outcomes of CVID?
If we identify, say, 10 genetic profiles, how accurately will this predict the PHENOTYPE, and help us to answer our patient’s question.

Common Questions
Can I develop the flu from the influenza vaccination?
Why do my lymph glands swell when I am sick?
Why don’t the bacteria on my food make me sick?
Can I take pills to “boost” my immune system?
What is “autoimmune” disease?
Why are more and more people developing allergies?

Towards a Healthy Immune System

- Adequate sleep
- Good nutrition
- Moderate exercise
- Enjoyment of life
- Hygiene

*Everything Grandma told you to do!*

(A healthy immune system cannot be purchased in a bottle)