Skin As An Immune Organ

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I have no conflicts of interest to declare!
Take Home Messages

• The immune system evolved to protect complex organisms from infection

• Immune responses are organismal, but compartmentalized

• Skin has “specialized” immune functions because it is an interface organ

• There is an active dialogue between the environment and the skin immune system that influences immune function

• *In vivo* studies are critical

• We know a lot, but we are still learning

• New information is altering existing paradigms, and impacting on patient care
How Does the Skin Immune System Work (I)?

• Keeps pathogens out
  • Stratum corneum, cell-cell and cell-matrix adhesion

• Recognizes and responds to breaches in the barrier and other “stresses”
  • Pathogen-unrelated (proinflammatory cytokine production 2° barrier disruption)
  • Danger signals (Innate Immune System)

• Prevents systemic dissemination of invading organisms
  • Skin intrinsic participants (anti-microbial peptides/defensins and structural elements)
  • Extrinsic participants (complement, leukocytes)
How Does the Skin Immune System Work (II)?

• Eliminate pathogens from inoculation sites
  • Innate and Adaptive Immune Systems

• Minimize damage to host tissues
  • Responses should of limited duration (counter-regulatory mechanisms)
  • Distinguish between non-self and self

• Remember the encounter and prevent another occurrence or attenuate severity
  • Adaptive Immunity
  • Circulating Antibodies (IgG)
  • Memory T cells (CD4 and CD8)
Discrimination Between Non-self and Self

• Innate Immune System
  • Pathogen-associated molecular patterns (microbes)
  • Pattern recognition receptors (host cells)
  • Self recognition receptors (inhibitory natural killer receptors)

• Adaptive Immune System
  • Central tolerance - mediated by deletion of autoreactive T cells in the thymus
  • Positive selection - T cells must recognize peptide-MHC complexes in the thymus to survive
  • Peripheral tolerance - active process mediated by regulatory T cells (CD4+ CD25+ Foxp3+ T cells, IL-10, TGFβ) and that may involve “unactivated” dendritic cells
Skin Barrier Function

• Skin is a dynamic, responsive interface between organism and environment

• The physical barrier is determined by properties of epidermal keratinocytes

• The air-liquid interface is largely maintained by a non-vital stratum corneum

• A sub-granular layer network of tight junctions regulates exchange of macromolecules, ions and water

• A constellation of immune and inflammatory cells, working in conjunction with resident skin cells, constitutes an immunologic barrier

• Perturbations of skin barrier function are common causes of, or aggravators of, skin diseases
Components of the Skin Immune System

- **Epidermis**
  - Keratinocytes
  - Dendritic cells (epidermal Langerhans cells)
  - Melanocytes and nerves (?)
  - Commensal microbes (?)
  - Lymphocytes (?)

- **Dermis**
  - Dermal dendritic cells
  - Lymphocytes (conventional and innate)
  - Mast cells
  - Natural killer (NK) cells
  - Endothelial cells (and vessels)

- **Subcutis (?)**
- **Regional lymph nodes**
- **Everything else (especially blood, bone marrow and spleen)**
Studying Immune Responses In Vivo

• Mice
  • Naturally occurring disease models
  • Transgenic mice
    • K14/IL-1
    • K14/TGFβRII
    • Langerin/DTR
  • Knockout mice
    • TGFβ
    • IL-12
    • IFNRI
    • Conditional (Cre-lox)
  • Knockin mice
    • Reporter gene (eYFP, ...)
    • Constitutive or conditional
  • Xenograft models
    • Psoriasis
  • Intravital microscopy or other real time imaging approaches

• Humans
  • Rare diseases (esp. monoallelic genetic diseases)
    • IPEX (Fox3p)
    • Atypical mycobacteria (IL-12R, NEMO)
    • DC-associated immuno-deficiency (IRF8)
    • Mono Mac (GATA2)
    • Pustular psoriasis (IL-36RA)
  • Biologic response modifiers
    • TNF reagents (TNF or TNFR)
    • Anti-Lymphocyte reagents (LFA-1, CD2, CD20)
    • Anti-T cell subpopulation reagents (CD25, CTLA4)
    • Anti-Cytokine reagents (IL-12/23 p40, IL-17)
  • GWAS
“Recent” Concepts

- Skin compartments are sites of residence of several leukocyte subpopulations (dendritic cells and T cells for example)

- Hair follicles have unanticipated immune regulatory functions and possible relevance to disease pathogenesis

- Commensal microbes regulate skin immune cell number and function
Fig. 1. Local skin infection leads to seeding of the entire skin surface with protective $T_{RM}$. After a localized skin infection with vaccinia virus in mice, highly protective virus-specific $T_{RM}$ were generated (1) that remained long-term in the skin and provided local protection against reinfection (21).

Highest number of $T_{RM}$ develop at the site of infection

Protective $T_{RM}$ in lower numbers colonize the rest of the skin surface

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Fig. 3. $T_{RM}$ are generated via a distinct, tissue-induced differentiation program.

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Tissue-resident T Cells

- Feature of tissues that interface with the environment
- $T_{RM}$, $T_{CM}$ and $T_{MM}$ generated during first exposures
- Both CD4 and CD8 T cells
- Repertoires are diverse
- Can be differentiated by surface phenotypes and expression profiles that indicate distinct functional characteristics
- $T_{RM}$ with potent effector function and accumulate in highest numbers at sites of initial pathogen exposure but also distribute to other skin sites and different epithelia
- $T_{CM}$ circulate systemically and serve as a precursor reservoir that can be tapped during reinfection/rechallenge
- $T_{MM}$ have intermediate levels of effector function and uncertain physiologic role currently
- Concept provides an intellectual framework for understanding a number of important skin diseases – psoriasis, MF/CTL, fixed drug reactions
Unanticipated Immunological Functions of Hair Follicles

MHC II
Recruitment of DC by Hair Follicle-derived Chemokines

Mechanical Stress

Infundibulum

Isthmus

Bulge

CCL2

CCL8

CCL20

Hair Follicle-derived Cytokines Regulate Resident Memory T Cells

Belkaid and Tamoutounour
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