IMMUNOLOGIC BASIS OF RINGWORM IN CHILDREN

Pauline LECERF, MD
Service de Dermatologie, CHU Brugmann,
CHU Saint-Pierre, Hôpital universitaire des Enfants Reine Fabiola
Université Libre de Bruxelles
INTRODUCTION

• Dermatophytes invade keratinized tissues
• Immune system and human skin work together
IMMUNE RESPONSE VARIABILITY

- According to the dermatophytes species
- Host species
- Pathophysiological status of the host
Dermatophytes species

• Anthropophilic species
  – Subtle, discrete, non inflamed infection
  – Chronic infection
  – Persistent, transferred from person to person

• Zoophilic, geophilic species
  – Intense inflammatory reaction,
  – Pustules, kerion
Differences between the Paediatric and Adult Immune Systems?

- Children do not make effective antibodies to polysaccharide antigens until around 5 years of age.
- Immune system grows and develops with the child until puberty.
- Sex hormones may be responsible for full maturation of the child’s immune system.
T. mentagrophytes
T. mentagrophytes
T. tonsurans
M. langeroni
T. soudanense
T. violaceum
HUMAN SKIN

Diagram showing layers of human skin:
- Epidermis
- Dermis
- Subcutaneous tissue (fat)

© Mayo Foundation for Medical Education and Research. All rights reserved.
EPIDERMIS
Dermatophytes and Immunity

• Dermatophytes induce

  1. Innate immunity (First-line of defence)

  2. Acquired immunity (Second-line)
INNATE IMMUNITY (First-Line)

- Prevention of pathogen’s invasion into the dermis
- Inflammation → Increase proliferatory activity of keratinocytes → fungus sloughed from the skin surface

Role of the keratinocytes and macrophages

• Adhesion and internalization of conidia
• Production of IL-1α, cytokines $\rightarrow$ inflammasome

• Anthropophilic species
  – Decrease keratinocyte’s production of IL-1α
  – kill macrophages (after internalized conidia differentiated in hyphae)
  – Modulate the activation program of the macrophage
  – Increase TNFα $\rightarrow$ induces intracellular proliferation

Role of the polynuclear neutrophils

- Production of cytokines and growth factor
- Enhancement of stratum corneum turnover → shed off the fungus from the skin surface
- Fungal growth inhibited
- Activate the complement (alternative pathway)

Role of the complement (alternative pathway)

- Activated by fungal cell wall or toxines when viable epidermis is invaded
- Cell membrane damage and phagocytosis
- Inhibition of fungal growth
- Intense neutrophilic reaction $\rightarrow$ pustules
- Anthropophilic species
  - Slight activation of the complement

Role of Langerhans cell

- Dendritic cell / Antigen-presenting cell
- Major histocompatibility complex
- Select LT CD4 or CD8
- Th1 or Th2 orientation

→ initiation and modulation of cell-mediated immunity

Dermatophytes and Immunity

• Dermatophytes induces

1. **Innate immunity** (First-line of defence)

2. **Acquired immunity** (Second-line)
   - Humoral
   - Cell-mediated
Humoral immunity

- Lymphocytes B
- Antibodies (IgG, IgM, IgA and IgE)
- No good evidence of protection
Cell mediated immunity (CMI)

• Delayed Type Hypersensitivity (DTH)
  – L Th1, IFNγ, macrophages, (Th17)
  – Intense inflammation → Acute infection
  – Clear dermatophytes from the skin
  – Trichophytin skin test = marker of DTH

• Immediate Hypersensitivity (IH)
  – L Th2, IL4, IgE, IgG4, mastocytes
  – Chronic infection

Role of the mannans

- Glycoproteins from the fungal cell wall
- Important virulence factor
- Variability between species
- Binds to monocytes’ cell surface receptors
  (→ subsequent phagocytosis impairment)
- Inhibits lymphoproliferation
- Inhibits keratinocyte proliferation
- Down regulate cell-mediated immunity
- Causes chronic infection

Role of the proteases

- Adhesion to the epidermis
- Digestion of the substrate
- Some proteases can induce a specific immune response:
  - Delayed Type Hypersensitivity → Acute infection
  - Immediate hypersensitivity → Chronic infection

- Subtilisin 3 (Sub 3) and metalloproteases 3 (Mep3) from *M. canis*; Tri r 2 : sub from *T. rubrum*; Tri t 4: sub from *T. tonsurans*

Clinical impact

• Development of immediate hypersensitivity (IH) versus delayed-type hypersensitivity (DTH) to *Trichophyton* allergens: pivotal to
  – course and severity of skin infection
  – development of allergic diseases.

Vermout. Mycopathologica 2008;
Clinical impact

- If innate and acquired immunity are **efficace** → **acute infection**, rapidly eliminated
- If **inefficacy** or pathogens well adapted to their host → **chronic infection** with little or no symptoms

- Examples
  - Chronic mocassin infection (weak DTH, High IgE)
  - Acute bullous *tinea pedis* (strong DTH, weak or no IgE)
CHRONIC INFECTION

• WHEN?
  – Dermatophytes outweigh the capabilities of cell-mediated immunity (Mannans, proteases)
  – Patient does not develop DTH against fungus but IH

Vermout. Mycopathologica 2008
Dermatophytosis and ALLERGY

• Chronic dermatophytosis (associated with IH skin test reactions) can contribute to the pathogenesis of allergic diseases, especially asthma

• Protease of T rubrum (Tri r 2) → allergen

• Example: Treatment of onychomycosis in patients with recalcitrant asthma

Dermatophytosis and ATOPY

• Atopic persons
  – Defective epidermal barrier
  – are more susceptible to mannan-induced suppression of CMI
  – Prone to develop immediate hypersensitivity (IH) → chronic infection

Vermout. Mycopathologica 2008
CONCLUSIONS

• Host-fungus relationship in these infections is complex and still poorly elucidated
• Protective immunity is a DTH (CMI)
• Serological tests in the future?
• Vaccines ? to help eradicate this infection or resolution of allergic symptoms
Thank you for your attention!
Dermatophyte’s antigen inducing immune response

Cell wall

Humoral immunity

β1,3
β1,6
glucans
PPL bilayer

Cell-mediated immunity

Keratinases

mannoproteins

β1,3 glucan synthase

chitin

ergosterol

Plasmic membrane
Annex

- Quantity of fungistatic saturated fatty acids in sebum increases at puberty
- Colonisation by *Pityrosporum orbiculare* may interfere with dermatophyte contamination
- Thicker calibre of adult hair may protect against dermatophyte invasion