Urticaria Pathogenesis

ARTrust™ and Stephen D. Lockey, Jr., MD Lecture

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Disclosures

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Objectives

• Review the pathophysiology of wheal and flare reactions and pruritus

• Understand the key pathogenic factors in chronic urticaria (CU)

• Understand the role of autoimmunity in CU
Pathophysiology of Wheal and Flare Responses

- Urticarial responses resemble wheal and flare reactions
- Erythema results from 2 factors:
  - Axon reflex (Flare)
  - Mediator-induced vasodilation
Pathophysiology Of Wheal

• Mediator-induced vascular permeability
  1. Formation of gaps via stimulation of endothelial cell receptors
  2. Increased permeability of cutaneous capillaries and postcapillary venules

• Persistence dependent upon:
  1. Time course of mediator action
  2. Rate of extravascular fluid drainage
Mediators And Wheal & Flare Responses

- Mediators causing wheal and flare
  - Histamine
  - Bradykinin
  - PGE$_2$/PGD$_2$
  - LTC$_4$/LTD$_4$/LTE$_4$
  - PAF
- Mediators causing prolonged erythema
  - PGE$_2$/PGD$_2$/PGI$_2$
- Mediators enhancing urticarial reactions
  - Proteases: increase vascular permeability
  - Chemotactic factors
  - Cytokines
Itch Associated Cells and Mediators

Cellular network of itch in the skin

Keratinocytes
release of:
NGF, NT-4 LTB₄, TXA₂
ET-1, eCB, β-endorphin

Mast cells
release of:
histamine, LTB₄, PGD₂,
proteases, NGF, IL-2
tryptase

Sensory nerves
release of:
SP, CGRP, ET-1, VIP

T cells
release of IL-31

Eosinophils
release of NGF

Nerve/Mast Cell Interactions in Pruritus

Key Pathogenic Factors of Chronic Urticaria

1. Mast Cells (Basophils)/Mediators

2. Histamine-releasing activity (non-Ig)

3. Neuropeptides via mast cell activation: Substance P, CGRP, VIP, and NGF

4. Inflammatory Cells Other Than Mast Cells/Basophils
Mast Cells (MCTc) and Urticaria

Altman and Chang; Clin Rev Allergy Immunol, 2013; 45:47.
Mast Cells (MCTc)/Basophils & Urticaria: Fulfilling Koch’s Postulates

- **Morphologic and histologic evidence:**
  - Mast cell degranulation evident
  - Exact role of basophils still unclear

- **Mediators induce wheal and flare.**

- **Mediators in biologic fluids during urticarial reactions.**

- **Mediator antagonists suppress urticaria.**
Cutaneous Allergen-Challenge Model

Evidence for role of Histamine and PGD$_2$

Skin Blister Model – response to ragweed allergen:

Charlesworth et al. JCI 1989
- Biphasic histamine, but not PGD$_2$, release (see top right)
- Eosinophils & basophils infiltrate 6-12 hrs post challenge

Pienkowski et al. JACI 1988
- 11/18 subjects had early & late phase response (LPR)
- LPR responders showed 6-fold higher levels of PGD$_2$ (see bottom right)
Role of Leukotrienes in Chronic Urticaria

Time course of LTD4 - Induced Wheal & Flare

Maxwell et al., J Allergy Clin Immunol 1990;86:759-765
Cold Urticaria Challenge Mediator Release

Maltby et al., Clin Exp Allergy 1989;19:33-36

Histamine (ng/ml plasma)

- Severe
- Severe
- Mild
- None
- None

Clinical Response to Challenge

LTE$_4$ (pg/ml plasma)

- Severe
- Severe
- Mild
- None
- None

Maltby et al., Clin Exp Allergy 1989;19:33-36
Differential Cutaneous Responses To Histamine in Chronic Urticaria

Skin Response to Intradermal Injection Hist, LTD4: 10^{-9} to 10^{-4}

Histopathology Of Chronic Urticaria

• The dermal perivascular infiltrate of lesional skin in CU contains mainly CD3⁺, CD4⁺, CD8⁺, and CD25⁺ T lymphocytes

• Cytokine profile: mRNA for IL-4, IL-5, and IGN-γ

• An intense perivascular neutrophilic infiltrate without vasculitis is seen in ~15% CU patients

Cells and Cytokines of CU

# Immune Profiles of CIU vs Normals

<table>
<thead>
<tr>
<th>Immune Cell Type/Tissue</th>
<th>Profile</th>
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<tbody>
<tr>
<td>Lymphocytes</td>
<td>Altered signaling through the p21Ras pathway&lt;sup&gt;42&lt;/sup&gt;</td>
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<td>Increased frequency of IL-10+ peripheral T cells&lt;sup&gt;43&lt;/sup&gt;</td>
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<td>Peripheral blood mononuclear cells (PBMC)</td>
<td>Increased stimulated production of TNF-α, IL-10, MIP-1α, and RANTES&lt;sup&gt;44&lt;/sup&gt;</td>
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<td>Reduced IL-4&lt;sup&gt;45&lt;/sup&gt;</td>
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<td>Peripheral blood dendritic cells (pDCs)</td>
<td>Impaired TLR9 induced interferon-α production&lt;sup&gt;46&lt;/sup&gt;</td>
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<td>Serum</td>
<td>Increased levels of TNF, IL-1β, IL-6, IL-13, IL-12p70, IL-10, and B-cell activating factor (BAFF); similar among those with CIU and CAU&lt;sup&gt;47–49&lt;/sup&gt;</td>
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<td>Increased IL-6, CRP in CU subjects with NSAID sensitivity after aspirin challenge&lt;sup&gt;50&lt;/sup&gt;</td>
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<td>Coagulation</td>
<td>Extrinsic coagulation pathway activated with increased levels of D-dimer and prothrombin fragments&lt;sup&gt;51&lt;/sup&gt;</td>
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The Central Role Of Mast Cells

Allergens
- Histamine
- IgE
- Mast Cell

Histamine, LTs, PGs

Histamine, PGD2, ILs, TNF-α

Chemokines

Autoantibodies
- C5a

Flare and Wheal
- Nerve cell
- SP, NKA, CGRP

Immune cell activation and recruitment
- Eosinophil
- Basophil
- Th2 cell

Wheal

Vasodilation and vascular permeability

Histamine

Blood vessel endothelium

Immune cell activation and recruitment

Inflammation
Altman and Chang; Clin Rev Allergy Immunol, 2013; 45:47.
Are There Intrinsic Differences In Mast Cells in CU Patients?

- Saini et al compared expression of SHIP-1, SHIP-2, and Syk protein to histamine release (HR) from mast cells (MC) cultured from the peripheral blood of CIU (treatment responsive) R, CIU (treatment nonresponsive) NR, and normal subjects.

Increased Spontaneous Histamine Release In CIU

CIU Patients Have Different Levels of Key Transcription Factors

A

SHIP-2

CIU R Std CIU NR Std Normal Std

SHIP-1

Syk

B

Relative Expression

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<td>SHIP 1</td>
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<td>Normal (n=7)</td>
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Therapeutic Implications: Targeting Syk

Chronic Autoimmune And Chronic Idiopathic Subtypes

• Both Have:
  – Lesions Lasting 4-36 Hrs
  – “Late Phase Response”

• Autoimmune (40-50%): Autoantibodies Vs. IgE Or FcεRIα (more common and specific)
  – IgG1 and 3 (role for complement)
  – Perivascular non-necrotizing infiltrate
  – Release Histamine from Mast Cells (In Vivo) and Basophils (In Vitro)
Autoimmune Chronic Urticaria

- Basopenenia
- Associated with:
  - HLA DR4
  - Hyper- and hypothyroidism (~2X)
    - Antimicrosomal Abs
    - Anti-TPO Abs
    - ATA may persist after CU remission
    - Treating thyroid disease does not “cure” CU
- Responsive to Plasmapheresis, IVIG, Cyclosporine, Omalizumab
Autologous Serum /Plasma Skin Test

0.05mL ID: (+) 1.5 cm>control at 30 min.

M. Greaves, JACI, 2000
Autoimmune Chronic Urticaria

- ASST due to both IgG auto-Abs and other (vasoactive) factors
  - Anti-IgE (~10%) not specific for CU
  - Anti-FceRI (30-40%) more specific for CU
  - ASST declines with therapy……but Ab titers do not correlate with disease activity
Increased De Novo PgD2 Secretion After Incubation Of CIU Derived Serum With LUVA Cells

What has Omalizumab Taught Us About Chronic Urticaria?

• The therapeutic efficacy of omalizumab pointed to an important role of IgE and FcεRI

• However, there are confounding issues:
  – Equal efficacy in patients with and without autoantibodies
  – Onset of action
Functional Autoantibodies of CAU

Complement activation & C5a Generation

Secretion

“LPR”

Infiltrative Hive

M. Greaves, JACI, 2000; A Kaplan, JACI, 2004
Onset Of Action Faster than Omalizumab’s Effect on FcεRI:
Many patients Improve within a few days

Lin et al. JACI; 2004;113;297
Maurer et al; NEJM; 2013; 368:924
Summary/Conclusion

• Mast cells are key effector cells in the pathogenesis of urticaria
• Targeting individual mast cell mediators is often not therapeutically effective
• Patients with CU likely have:
  – Circulating factors (both Ig and non-Ig) that promote mast cell degranulation
  – Intrinsic differences in mast cells
• The role of autoimmune mechanisms and how omalizumab works in CU are not totally understood