Understanding How Allergic Responses End: The Allergy Resolvome

Koichiro Asano, MD
Ariel Munitz, PhD
**Learning objectives:**
- Identify factors involved in resolution of inflammation
- Review lipid mediators
- Review IL-10 and endocannabinoids mechanism of action in the resolution of inflammation

**Session overview:**
1. Introduction to inflammation and allergic inflammation  
   5-10 min
2. Anti-inflammatory and pro-resolution lipid mediators  
   25 min
3. IL-10 and allergic inflammation  
   10-15 min
4. Cannabinoids  
   10 min
Inflammation - a complex physiological process in response to local injury or trauma involving various **cells** and **mediators**

- **Calor** (Heat)
- **Rubor** (Redness)
- **Tumor** (Swelling)
- **Dolor** (Pain)
- **Functio laesa** (Loss of function)
Sequential order of an inflammatory response

Trauma → Vasodilation (minutes) → Increased blood flow to the tissue → Heat and redness → Edema → Leukocyte extravasation → Chronicity (Fibrosis) → Healing

Vascular response

Phagocyte response → Pain and loss of function
The inflammatory response is mediated by various **cells**

**Hematopoietic cells**
- Resident cells
  - Macrophages
  - Mast cells
  - Innate immune cells
- Recruited cells
  - Neutrophils/Eosinophils
  - Monocytes
  - Lymphocytes

**Structural cells**
- Endothelial cells
- Epithelial cells
- Fibroblasts
What are the roles of inflammation?

1. Deliver effector cells to the inflammatory site

Saline:  WT

OVA:  WT
What are the roles of inflammation?

2. Containment of infection (clotting system, ECM, granuloma)
What are the roles of inflammation?

3. Tissue healing and repair
The allergic/inflammatory response

Sensitization

Allergen

Antigen presenting cell (APC)

“Education” (IL-33, TSLP, IL-25)

CD4+ T-helper cell

MHC-II

TCR complex

IgE

B-cell

IgE

FcεRI

Tissue Mast cell

Eosinophil

CCR3

Fibroblasts

Epithelial Cells

SM cells

Healing processes are an integral component of the inflammatory cascade
The local clinical signs of inflammation
Anti-inflammatory and pro-resolution lipid mediators
## IL-10 family cytokines

<table>
<thead>
<tr>
<th>Name</th>
<th>Chromosome location (human)</th>
<th>Structure</th>
<th>Receptor</th>
<th>Major cellular sources</th>
<th>Cellular targets</th>
<th>Key functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-10</td>
<td>1q32</td>
<td>Dimer</td>
<td>IL-10R1/IL-10R2</td>
<td>Leukocytes</td>
<td>Leukocytes</td>
<td>Immune repression</td>
</tr>
<tr>
<td>IL-19</td>
<td></td>
<td>Monomer</td>
<td>IL-20R1/IL-20R2</td>
<td>Myeloid cells, epithelial cells</td>
<td>Epithelial cells</td>
<td>Antibacterial responses, tissue remodeling, wound healing</td>
</tr>
<tr>
<td>IL-20</td>
<td></td>
<td>Monomer</td>
<td>IL-20R1/IL-22R</td>
<td>Myeloid cells, epithelial cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-24</td>
<td></td>
<td>Monomer</td>
<td></td>
<td>Myeloid cells, epithelial cells Th2 cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-22</td>
<td>12q16</td>
<td>Monomer</td>
<td>IL-22R/IL-10R2</td>
<td>T cells, NK cells, NKT cells, L'Ti cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-26</td>
<td></td>
<td>Dimer?</td>
<td>IL-20R1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-28A</td>
<td>19q13</td>
<td>Monomer</td>
<td>IL-28R</td>
<td>Leukocytes, epithelial cells</td>
<td>Epithelial cells, leukocytes?</td>
<td>Antiviral responses</td>
</tr>
<tr>
<td>IL-28B</td>
<td></td>
<td>Monomer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-29</td>
<td></td>
<td>Monomer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cellular sources for IL-10 expression

Source #1: Myeloid cells
Cellular sources for IL-10 expression

Source #1: T helper cells
Cellular sources for IL-10 expression

**Source #1:** Treg cells

- FOXP3$^+$ T$_{reg}$ cell
- FOXP3$^-$ naive T cell
- TGFβ and retinoic acid

- IL-10-producing FOXP3$^+$ T$_{reg}$ cell
- IL-10-producing FOXP3$^-$ regulatory T cell

Nature Rev Immunol
VOLUME 10 | MARCH 2010 | 171
IL-10 receptor and signaling

Effector functions of IL-10 in allergy

- **Dendritic cell**
  - Pro-inflammatory cytokine production
  - MHC class II and co-stimulatory molecule expression
  - Maturation
  - APC function for promoting T-cell proliferation and cytokine production

- **Mast cell**
  - Fc receptor

- **Eosinophil**
  - Survival
  - Cytokine production

- **B cell**
  - IgE production
  - Favourable modulation of IgG4 to IgE ratio

- **IL-10-secreting regulatory T cell**
  - IL-10 production

- **IL-10**

- **Nature Rev Immunol**
  - 276 | APRIL 2005 | VOLUME 5
Allergen specific immunotherapy and IL-10

↓ Allergen-specific IgE
↓ Seasonal increases in IgE
↑ Blocking antibodies: IgG1, IgG4 and IgA
↑ IL-10

↓ Allergen-specific proliferation
↓ Tissue numbers in late-phase reactions
↓ T_{H2}-cell cytokines in tissues
↑ T_{H1}-cell cytokines in tissues
↑ T_{Reg} cells, IL-10 and TGFβ

↑ IL-10

Monocyte

T cell

B cell

SIT

Eosinophil

Mast cell

↓ Tissue numbers
↓ Mediator release
Cannabinoid-based drugs as anti-inflammatory therapy
What are cannabinoids?
<table>
<thead>
<tr>
<th>Endocannabinoids</th>
<th>Natural cannabinoids</th>
<th>Synthetic cannabinoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arachidonyl ethanolamide</td>
<td>$\Delta^9$-tetrahydrobannbinol</td>
<td>JWH-133</td>
</tr>
<tr>
<td>2-arachidonoylglycerol</td>
<td>Cannabidiol</td>
<td>WIN55,212-2</td>
</tr>
</tbody>
</table>

![Chemical structures](image)
Cannabinoid receptors and signal transduction 1
Cannabinoid receptors and signal transduction 1
Induction of CB and CB receptors in inflammatory settings
Table 2 | Cannabinoid effects on adaptive immunity and T helper cells

<table>
<thead>
<tr>
<th>Cannabinoid</th>
<th>Receptor</th>
<th>Cell or tissue type</th>
<th>Cytokine stimulant or inflammation model</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mice</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THC</td>
<td>ND</td>
<td>Spleen</td>
<td>Legionella pneumophila</td>
<td>Decreases IFN-γ and IgG2a</td>
<td>70</td>
</tr>
<tr>
<td>THC</td>
<td>CB&lt;sub&gt;1&lt;/sub&gt; and CB&lt;sub&gt;2&lt;/sub&gt; dependent</td>
<td>Spleen</td>
<td>Legionella pneumophila</td>
<td>Decreases IL-12 and IL-12R and increases IL-4</td>
<td>71</td>
</tr>
<tr>
<td>THC</td>
<td>CB&lt;sub&gt;2&lt;/sub&gt; dependent</td>
<td>Spleen</td>
<td>Tumour model</td>
<td>Decreases IFN-γ and increases IL-10 and TGF-β</td>
<td>73</td>
</tr>
<tr>
<td>WIN55,212-2</td>
<td>ND</td>
<td>Spleen</td>
<td>Thielors’s murine encephalomyelitis virus</td>
<td>Decreases IFN-γ</td>
<td>78</td>
</tr>
<tr>
<td><strong>Humans</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THC</td>
<td>CB&lt;sub&gt;2&lt;/sub&gt; dependent</td>
<td>Peripheral-blood T cells</td>
<td>Allogeneic dendritic cells</td>
<td>Decreases IFN-γ</td>
<td>76</td>
</tr>
<tr>
<td>Marijuana smoking</td>
<td>ND</td>
<td>Peripheral-blood mononuclear cells</td>
<td>Phytohaemagglutinin and concannavalin A</td>
<td>Decreases IL-2 and increases IL-10 and TGF-β</td>
<td>77</td>
</tr>
</tbody>
</table>

CB, cannabinoid receptor; IFN-γ, interferon-γ; IL, interleukin; IL-12R, IL-12 receptor; ND, not determined; TGF-β, transforming growth factor-β; THC, Δ⁹-tetrahydrocannabinol.
Effect of cannabinoids on cytokine and chemokine production.

<table>
<thead>
<tr>
<th>Cannabinoid</th>
<th>Receptor</th>
<th>Cell/tissue/serum</th>
<th>Effect</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC</td>
<td>ND</td>
<td>Macrophage cell line (RAW264.7)</td>
<td>Decreases TNF-α</td>
<td>[40]</td>
</tr>
<tr>
<td>THC</td>
<td>ND</td>
<td>Peritoneal macrophages</td>
<td>Increases IL-1α and IL-1β</td>
<td>[41]</td>
</tr>
<tr>
<td>THC</td>
<td>ND</td>
<td>Human cell lines</td>
<td>Decreases TNF-α, GM-CSF and IFN-γ, IL-10,</td>
<td>Increases IL-8</td>
</tr>
<tr>
<td>THC</td>
<td>CB1 and CB2 independent</td>
<td>Rat microglial cells</td>
<td>Decreases TNF-α, IL-1α, IL-1β and IL-6</td>
<td>[28]</td>
</tr>
<tr>
<td>In vivo WIN55,212-2 and HU-210</td>
<td>CB1 dependent</td>
<td>Serum</td>
<td>Decreases TNF-α, IL-12</td>
<td>Increases IL-10</td>
</tr>
<tr>
<td>Cannabidiol</td>
<td>ND</td>
<td>Human synovial monocyte-derived macrophage</td>
<td>Decreases IL-6 and IL-1β</td>
<td>[32]</td>
</tr>
<tr>
<td>HU-308</td>
<td>CB2 dependent</td>
<td>Serum and liver homogenates</td>
<td>Decreases TNF-α, MIP-1α and MIP-2</td>
<td>[33]</td>
</tr>
<tr>
<td>CP55,940 WIN55,212-2</td>
<td>CB1 and CB2 independent</td>
<td>Rheumatoid fibroblast-like synoviocytes</td>
<td>IL-6 and IL-8</td>
<td>[34]</td>
</tr>
<tr>
<td>2-AG</td>
<td>CB2 dependent</td>
<td>Promyelocytic leukemia cell line (HL-60)</td>
<td>Increases IL-8, CXCL8 and CCL2</td>
<td>[37]</td>
</tr>
</tbody>
</table>

AG: Arachidonylglycerol; CB: Cannabinoid receptor; CCL: CC-chemokine ligand; CXCL8: CXC-chemokine ligand 8; ND: Not determined; THC: Tetrahydrocannabinol.
<table>
<thead>
<tr>
<th>Table 3</th>
<th>Preclinical and clinical studies examining the anti-inflammatory effects of cannabinoids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nervous tissue inflammation</strong></td>
<td>Drugs</td>
</tr>
<tr>
<td>EAE in rats and guinea pigs</td>
<td>THC</td>
</tr>
<tr>
<td>EAE in rats</td>
<td>THC</td>
</tr>
<tr>
<td>Thal’s murine encephalomyelitis-virus-induced EAE in mice</td>
<td>WIN55,212-2</td>
</tr>
<tr>
<td>Thal’s murine encephalomyelitis-virus-induced EAE in mice</td>
<td>WIN55,212-2, ACEA, or JWH-015</td>
</tr>
<tr>
<td>Neuropathic pain in rats</td>
<td>AM251</td>
</tr>
<tr>
<td>Closed head injury in mice</td>
<td>2-AG</td>
</tr>
<tr>
<td>Closed head injury in rats</td>
<td>HU-211</td>
</tr>
<tr>
<td><strong>Inflammatory bowel disease</strong></td>
<td></td>
</tr>
<tr>
<td>LPS-induced gastrointestinal transit in rats</td>
<td>ACEA or JWH-133</td>
</tr>
<tr>
<td>Chemically induced colitis in mice</td>
<td>HU-210</td>
</tr>
<tr>
<td><strong>Arthritis</strong></td>
<td></td>
</tr>
<tr>
<td>Leukocyte influx in mice and adjuvant-induced arthritis in rats</td>
<td>Aullemic acid</td>
</tr>
<tr>
<td>PBMCs and synovial-fluid monocytes</td>
<td>Aullemic acid</td>
</tr>
<tr>
<td>Collagen-induced arthritis in mice</td>
<td>Cannabidiol</td>
</tr>
<tr>
<td>Collagen-induced arthritis in mice</td>
<td>HU-330</td>
</tr>
<tr>
<td><strong>Vascular inflammation</strong></td>
<td></td>
</tr>
<tr>
<td>LPS-induced hypotension in rats</td>
<td>SR141716A</td>
</tr>
<tr>
<td>Myocardial ischamia-reperfusion injury in mice</td>
<td>WIN55,212-2</td>
</tr>
<tr>
<td>Septic shock in mice</td>
<td>HU-211</td>
</tr>
</tbody>
</table>

ACEA, acetylcholine acetylcholine; 2-AG, 2-arachidonoylglycerol; CB, cannabinoid receptor; CNS, central nervous system; DTH, delayed-type hypersensitivity; EAE, experimental allergic encephalomyelitis; IFN-γ, interferon γ; IL-1β, interleukin-1β; LPS, lipopolysaccharide; PBMC, peripheral blood mononuclear cell; THC, 1-tetrahydrocannabinol; TNF, tumour-necrosis factor.
Attenuation of the ovalbumin-induced allergic airway response by cannabinoid treatment in A/J mice☆

Tong-Rong Jan,a,† Aimen K. Farraj,a Jack R. Harkema,b and Norbert E. Kaminskia,*

a Department of Pharmacology and Toxicology, National Food Safety and Toxicology Center, Michigan State University, East Lansing, MI 48824, USA
b Department of Pathobiology and Diagnostic Investigation, National Food Safety and Toxicology Center, Michigan State University, East Lansing, MI 48824, USA

Received 12 July 2002; accepted 19 December 2002

(A) Single Challenge

Ovalbumin Sensitization → Ovalbumin Challenge → Sacrifice

Day -3 -2 -1 0 11 12 13 14 15

CBN, ∆⁹-THC and/or VH

(B) Double Challenge

Ovalbumin Sensitization → Ovalbumin Challenge → Ovalbumin Challenge → Sacrifice

Day -3 -2 -1 0 11 12 13 14 21 22 23 24 28

CBN, ∆⁹-THC and/or VH
CBN and THC attenuate allergen-induced IL-4 production
CBN and THC attenuate allergen-induced IgE expression
CBN and THC attenuate allergen-induced mucus production