Endocannabinoid signalling at the skin/immune cell interface

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Molecular architecture of the endocannabinoid system (ECS) in the brain

Anatomy of the epidermis

- Dead cells flaking off at the skin surface
- Stratum corneum
- Stratum lucidum
- Stratum granulosum
- Stratum spinosum
- Stratum basale
- Dermis

Keratinocytes move up as they age
- Dead keratinocyte
- Lamellar granules
- Langerhans cell
- Keratinocyte
- Melanin
- Melanocyte
- Merkel cell
- Basal lamina

Stratum corneum
Granular cell layer
Spinous layer
Basal layer
### Expression of the ECS in the skin

<table>
<thead>
<tr>
<th>ECS member</th>
<th>Epidermis</th>
<th>Dermis</th>
<th>Nerve fibers</th>
<th>Adnexal structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB₁</td>
<td>Suprabasal keratinocytes; primary melanocytes</td>
<td>Fibroblasts, mast cells, macrophages</td>
<td>Single epidermal nerve fibers, small unmyelinated subepidermal nerves, large dermal myelinated nerves</td>
<td>Differentiated sebocytes, differentiated epithelial cells of the infundibulum and inner root sheath of hair follicles, myoepithelial cells of eccrine sweat glands, sweat gland duct</td>
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<td>Fibroblasts, mast cells; vascular smooth muscle cells</td>
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<td>AEA</td>
<td>Primary keratinocytes and melanocytes</td>
<td>Macrophages</td>
<td></td>
<td>Human sebocytes SZ95</td>
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<td>2-AG</td>
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<tr>
<td>NAPE-PLD</td>
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<td>Primary fibroblasts</td>
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Oddi and Maccarrone, *Handbook of Cannabis* 2014
Cutaneous eCB signalling

Maccarrone et al., TiPS 2015
The melanoma revolution: From UV carcinogenesis to a new era in therapeutics

Jennifer A. Lo and David E. Fisher

SCIENCE 21 NOVEMBER 2014 • VOL 346 ISSUE 6212
Melanoma development, melanogenesis and eCB signalling

Pucci et al., J.B.C. 2012
Maccarrone, Science 2015
Epigenetic control of skin differentiation genes by phytocannabinoids

Mariangela Pucci1*, Cinzia Rapino1*, Andrea Di Francesco1, Enrico Dainese1,2, Claudio D’Addario1 and Mauro Maccarrone2,3
Epigenetic regulation: a new clue to endocannabinoid activity?

Genetics vs Epigenetics

Genetic Mutations Often Alter Meaning
A gene's nucleotides (code letters) form a blueprint for a protein (top). A wrong letter or other mutation can derange the resulting protein (bottom) or cause too much or too little to be made.

Epigenetic Changes Alter Activity
Chemical tags known as epigenetic marks sit atop genes, either on the DNA itself or on the histone proteins around which DNA is wrapped (below). Changes in the mix of these marks can alter a gene's behavior, turning the gene on or off, so that protein synthesis is inhibited, or turning it on—all without changing the information the gene contains.
Endocannabinoids can regulate (and be regulated by) epigenetic mechanisms.
Epigenomic signatures of disease can boost drug development

The Roadmap Epigenomics Project opens new drug development avenues

The US National Institutes of Health’s US$240-million epigenomics investment could improve the study of disease biology, the identification of new drug targets, the validation of animal models and more.

Mullard et al., NRDD 2015
Skin/immune cell interface

- Langerhans cell
- Keratinocyte
- DETC
- Stratum corneum
- Epidermis
- Dermis
- Lymphatic vessel
- Fibroblast
- Melanocyte
- CD8+ T cell
- Neutrophil
- Mast cell
- Macrophage
- CD4+ T cell
- Dermal dendritic cell
- CLA+ effector T cells
- CCL17
- E-selectin
- ICAM1
- Dermal post-capillary venule
- Antigen
- Activated Langerhans cell
- Inflammation
- Cytokine and chemokine release by LCs and keratinocytes
- Recruitment of CLA+ effector T cells
- Production of chemokines and cytokines
- Peptide-MHC
- TCR
- Naive/memory T cell
- Granulocyte
Immune T cells

Physical Triggers of Immune Response:
- Infections
  - Bacterial, viral
  - Fungal, parasitic
- Toxins
  - Exogenous
  - Endogenous
- Food peptides
- Allergens
- Medications
- Auto antigens

Th0: Naive T cells
Th: Helper T cells
Treg: Regulatory T cells
IL: Interleukin
TNF-α: Tumor necrosis factor-alpha
IFN-γ: Interferon-gamma
TGF-β: Transforming growth factor-beta

Th1:
- Extracellular bacteria
  (skin, lining of intestine)
- Fungi
- Autoimmunity

Th17:
- Cell-mediated immunity and inflammation
- Intracellular pathogens
  - Viruses, bacteria
- Autoimmunity
- Inflammation

Th2:
- Antibody-mediated immunity
- Extracellular parasites
- Asthma, allergy

Treg:
- Immune tolerance
- Lymphocyte homeostasis
- Regulation of immune responses

Antigen Presenting Cells

Th0

Th17
- IL-17
- IL-21
- IL-22

Th1
- IL-2
- IFN-γ
- TNF-α

Th2
- IL-4
- IL-5
- IL-6
- IL-10
- IL-13

TGF-β, IL-6

Naive T cell

Th0
- TGF-β, IL-12
- IL-4, IL-2

Immune T cells
Role of T cells in skin diseases
Endocannabinoid signalling in innate and adaptive immunity

Chiurchiù et al., Immunology 2015