Restoring Immune and Stem Cell Function and Homeostasis Using Natural Remedies and Purinergic Therapy

Waking to a New Dawn: The Emergence of 21st Century Acquired Immune Deficiencies & Innovative Solutions

Judy A. Mikovits, PhD
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www.marcinc.org
1980  Discovery of HTLV-I

Pathogenesis:
- Asymptomatic in majority of individuals
- 5% lifetime risk of developing either type of disease:
  - Adult T cell leukemia
    - Clonal malignancy of CD4⁺ T cells.
    - Long latency; Immune deficiency
  - Inflammatory syndromes not realized until decades later
  - HTLV-I associated myelopathy/Tropical spastic paraparesis
  - Uveitis
  - Arthropathy
  - Sjogren’s Syndrome
Many Factors important in Development of Chronic Diseases associated with Retroviruses

HAM/TSP Usually Chronic Slowly progressing

- Northeastern Brazil: rapid progression Necessitating Wheelchair in 2 Years
- 8% had rapid progression: Peru 21% had rapid progression
- No difference in Viral Load
- Early Recognition is critical, immune suppressive therapy BENEFICIAL EARLY
Immunity is not static: it changes with age; many unique features in early life

The Brain and The Immune System are inextricably linked from Conception
Monocyte/Macrophage as the Driver of AIDS

- Express Purinergic Receptors: P2XR and P2YR.

Tissue Macrophages perform Key Homeostatic Functions Modulated by
- Cannabinoids
- Suramin
- Flavonoids Baicalein, Quercetin
- GcMAF(Rerum)
Microglia Activation in Neurodegeneration

Stimuli
Loss of cell:cell communication, matrix breakdown, infections, vascular damage, others

Homeostasis
Phagocytosis of debris, neurotrophins

ANGRY
Damage
Neurotoxins, phagocytosis of normal neurons, apoptosis

Neurodegenerative disorders
- Parkinson's disease
- Alzheimer's disease
- Multiple sclerosis
- Autism
- ME/CFS

HAPPY
Phagocytosis of debris, neurotrophins

Resting (ramified) microglia

Activated (amoeboid) microglia

Fetler, L and S Amigorena, Science 2005, 309:392
Differential inhibitory effects of various flavonoids on the activities of reverse transcriptase and cellular DNA and RNA polymerases

Katsuhiko ONO¹, Hideo NAKANE¹, Masanori FUKUSHIMA², Jean-Claude CHERMANN³ and Françoise BARRÉ-SINOUSI⁴

Baicalein

Quercetin

Quercetagetin

Myricetin
MAST cell a Rheostat? Modulates Type and amplitude of innate and adaptive Immune
Interactions among mast cells–microglia–neurons and the blood–brain barrier
Many viruses use DC to facilitate spread:
- Some viruses infect DC, then are transmitted to target cells
- Other viruses are transmitted by DC without infection

Viruses can interfere with immune responses:
- Inhibit maturation and/or migration of immature DC
- Alter cytokine/chemokine production
- Cause apoptosis
- Impair (or enhance) DC function
Brain Homeostasis Maintained by Danger Signals
Nitrogenous bases of DNA
Deoxyadenosine
Deoxyguanine
Purinergic Signaling plays a critical Role In Chemotaxis of Multiple Cell Types
Pathophysiology of Purinergic Signaling

**Macrophages**
- M1: P2X4, A2A, BDNF release, PGE2 release, «M2 phenotype» differentiation
- M2: VEGF release

**T Cells**
- T cell: differentiation
- Treg: P2R, differentiation
- Th17: P2R, differentiation

**MDSC**
- ROS, IL-1β, Arg-1, TGF-β

**Microglial Cells**
- UDP: phagocytosis
- P2Y6, P2X7
- ATP: classic cation, P2Y10

**Dendritic Cells**
- Immature DC
- «tumor promoting phenotype» differentiation
- «Th2-skewing phenotype» differentiation
- VEGF release, Tumor Ag presentation
CD39 and CD73 in immunity and inflammation

Luca Antonioli¹,², Pál Pacher³, E. Sylvester Vizi⁴,⁵, and György Haskó²
¹Department of Clinical and Experimental Medicine, University of Pisa, 56126 Pisa, Italy

Highlights

CD39 and CD73 are important for calibrating the duration, magnitude, and composition of the “purinergic halo” surrounding immune cells

CD39 and CD73 degrade ATP, ADP and AMP to adenosine, they can be viewed as “immunological switches” that shift ATP-driven pro-inflammatory immune cell activity toward an anti-inflammatory state mediated by adenosine

CD39 and CD73 are highly expressed on the surface of Foxp3+ Tregs and have been increasingly used as markers of Tregs

CD39 and CD73 are important for the immunosuppressive activity of Tregs

CD39 and CD73 generate an immunosuppressed environment, characterized by increased adenosine levels, which promotes the development and progression of cancer
Adenosine produced by enzymatic Activity of CD39 implicated in progressive immunosuppression HIV/AIDS

P2Y receptor (P2YR) inhibitor (Suramin) critical response to Tissue injury
Suramin: on WHO list of Essential Medicines needed in a Basic Health System

- Antiparasitic 1920s
- Potent RT inhibitor 1986
- P2Y Purinergic Receptor inhibitor
- Cancer therapy prostate cancer, HTLV-1 cancer Bladder Cancer

- Inhibit the binding of growth factors (TGF-beta, EGF, PDGF to their receptors and thus antagonize the ability of these factors to stimulate growth of tumor cells
Purinergic signaling neural and Mesenchymal Stem Cell Maintenance and Differentiation

- Astrocyte: respond to ATP/ADP with migration, proliferation, neuronal differentiation, apoptosis, and a decrease in proliferation.

- NPC: respond to ATP/ADP with migration, proliferation, and neuronal differentiation.


- Osteoblasts: express P2X1 and P2Y1.

- Osteocytes: express P2X7, P2Y2, P2Y6, A2A, P2Y1, P2Y4, P2Y11.

- Adipocytes: express P2Y1 and P2Y11.
Review

Cannabinoid receptor signaling in progenitor/stem cell proliferation and differentiation

Ismael Galve-Roperh, Valerio Chiurchiù, Javier Díaz-Alonso, Monica Bari, Manuel Guzmán, Mauro Maccarrone

a Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, IJIN, CIBERNED and IRYCIS, 28040 Madrid, Spain
b Department of Biomedical Sciences, University of Teramo, 64100 Teramo, Italy
c European Center for Brain Research (CERC)/Santa Lucia Foundation, 00143 Rome, Italy
d Department of Experimental Medicine & Surgery, Tor Vergata University of Rome, 00133 Rome, Italy
e Center of Integrated Research, Campus Bio-Medico University of Rome, 00128 Rome, Italy
TGF-β is a Master Regulator of the Hematopoietic Stem Cell
Cannabinoid Receptor Activation of Macrophages

Is Purinergic Signaling the Driver of Development of Myelosuppressive (MDSC)/and Tumor associated Macrophages (TAM)?
Induction of CB2 on Lymphocytes is THC dependent
Cannabinoids are Anti-Viral and Reduce Neuroinflammation
CB2 is associated with Chronic inflammation of the nervous system, Cardiovascular and Bone Disorders
Neuroprotection by Endocannabinoid Modulation in Neurodegenerative Disease
• Tolerance to pain-blocking effects of opiates
• Depression and anxiety in chronic pain
• Negative effects of cannabis on memory
• Parkinson’s and Huntington’s Disease
• Cancer cell metastasis
Crosstalk between Purinergic receptors and cannabinoid Receptors regulates Microglia
Plant Derived- Phytocannabinoids
Phyto-cannabinoids Dampen Tissue Injury to Prevent Progression of Neurodegenerative Disease and Cancer

- Neurotrauma
- Ischaemia
- Major Depression
- Alzheimer’s Disease
- Parkinson’s Disease
- Amyotrophic Lateral Sclerosis
- Multiple Sclerosis

- Cytokines
- Chemokines
- Growth Factors
- Neurotransmitters
- Neurohormones
- Free Radicals
- ROS Scavengers
- Energy Substrates
Restoring Gut Homeostasis

- Cannabinoids/EndoCannabinoids
- Bone Broth organixx.com
- Camels Milk
- BRAVO Yogurt Probiotic /Restore
- Essential Oils
The endocannabinoid system is involved in immunoregulation and neuroprotection. Cannabinoid receptors crosstalk with Purinergic Receptors

Dysregulation of Endocannabinoid and Purinergic signaling by Overstimulation of Immune system by vaccines containing retroviruses and toxins (AL, Glyphosate) is causative for cancer Autoimmune neuroimmune diseases

Lipid mediators of the Endocannabinoid System and their receptors exert pleiotropic and complex immunoregulatory effects.

Endocannabinoids are master regulators of the innate adaptive-immune axis.

The effect of endocannabinoids on the orchestrators of the immune response, the monocyte/macrophage, is a key therapeutic target to modulate sterile inflammation and protect tissues from damage from excessive inflammatory mediators.

Combination therapies using Suramin (and other modulators of purinergic signaling) and cannabinoids can be curative therapies for 21st Century AIDS
Dysregulation of cannabinoid receptor signalling in glioma cells.

Programming of neural cells by (endo)cannabinoids: from physiological rules to emerging therapies