Immuno-metabolics Implications in Pediatric Rheumatology

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Objective

- To familiarize clinicians with the Physiology of Immuno-metabolics
- To demonstrate the clinical implications of Immuno-metabolics in Pediatric Rheumatology
Outline

- Definition of Immuno-metabolics
- Physiology of Immuno-metabolics
- Implications of Immuno-metabolics in Pediatric Rheumatology
Definition

- Distinct synergistic pathways and cellular reactions that impact on the activation of signaling and modification of cellular processes among cells of the body’s defence system.

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Introduction

- Cellular metabolism is necessary for generating energy and sustaining life.

- Through a series of steps involved in glycolysis (glucose), fatty acid oxidation, and amino acid (protein) oxidation, cells can break down ingested products into critical energy sources.

The interplay between metabolic pathways and immune cells leads to a plethora of different signaling pathways as well as cellular activities.

However, tight regulation of immune cell metabolism is required for protecting the host and resuming homeostasis.

An imbalance of immunological metabolic function and/or metabolic byproducts (reactive oxygen species) can often times lead to diseases.

Introduction

- In the case of cancer, overactive glucose metabolism can lead to hyperproliferation of cells and subsequent decreases in cytotoxic T cell activity, which attack and destroy the tumor.

- For this reason and many more, targeting metabolism in immune cells may be a novel therapeutic strategy for treatment of disease.

Introduction
Physiology of Immuno-metabolics

Figure 2: T cell differentiation is accompanied by metabolic changes, which are affected by costimulatory and coinhibitory receptors. Naive T cells function in antigenic surveillance and do not proliferate. This requires minimal energetic and biosynthetic activity, which is represented by a metabolically quiescent state, and is accompanied by minimal nutrient uptake. Their only energy-demanding processes are ion homeostasis, membrane integrity, and movement. The primary ATP sources are oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) to fuel the low energy demand. Upon antigen encounter, T cells differentiate into effector cells. This process is accompanied by metabolic changes, which are required to fulfill their new (effector) functions and rapid proliferation. Uptake of nutrients is enhanced. Glucose is the main nutrient used for energy and for generation of biosynthetic precursors. These changes combined with increased glutaminolysis and a high degree of protein, lipid, and nucleic acid synthesis support cell growth and proliferation. These metabolic changes coincide with mitochondrial fusion. Memory T cells do not proliferate and thus have minimal biosynthesis and nutrient uptake. However, they have increased spare respiratory capacity, which supports their ability to rapidly proliferate upon re-encounter of antigen. This cellular fate includes another metabolic adaptation, which supports metabolic switch to FAO via increased carnitine palmitoyltransferase 1A. These metabolic and energetic changes are supported by fusion of mitochondria.
The electron transport chain is also responsible for the formation of mitochondrial reactive oxygen species (ROS) through continuous ‘leakage’ of electrons, causing partial reduction of O2 molecules.

Generation of superoxide (SO2), hydrogen peroxide (H2O2), and hydroxyl radical (OH-), which can both stimulate physiological actions as well as damage important molecules in the body, depending on the quantity.

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Int J Biochem Cell Biol 2007;39:44-84
Clinical and Experimental Immunology, 184: 197–207
Ros production is, thus, a necessary evil for functional aerobic metabolism.

Am J Clin Exp Immunol 2013;2(1):30-54
Clinical and Experimental Immunology, 184: 197–207
In addition to housekeeping proliferation and sustenance, ATP within the immune cells must be ready to carry out effector responses.

Effector responses are thermodynamically taxing.

Furthermore, immune cells must facilitate
- cytoskeletal changes,
- increased ion signaling,
- enhanced phospholipid turnover, and
- greater macromolecule synthesis in a very short time during rapid energy consumption.

Am J Clin Exp Immunol 2013;2(1):30-54
Physiology of Immunometabolics

- Dendritic cells, for example, are known to undergo metabolic changes towards greater glycolysis upon toll-like receptor (TLR) stimulation.

- Lymphocytes rely on oxidative phosphorylation during resting states but switch to glycolysis during activation.

- Aerobic glycolysis ensures that enough energy is made to propel macromolecule synthesis (anabolic metabolism), which is ultimately crucial for clearance of a pathogen.

Physiology of Immunometabolics
Clinical Implications
Implications in Rheumatology

- CD28 is the quintessential costimulatory molecule for T cell activation. Its ability to bind CD80/CD86 on APCs enables downstream signaling and promotes T cell differentiation.

- CD28 has been shown to enhance glucose metabolism by triggering accumulation of glycolytic intermediates stimulating glycolysis, and increasing glucose transporter expression.

- CTLA-4 on the other hand, offsets the effects of CD28, reducing glycolysis and rendering cells quiescent.

Abatacept modulates the immune response by binding to CD80/CD86 on an antigen-presenting cell (APC), such as a dendritic cell, thus preventing costimulatory binding of CD28 on naive T cells and attenuating T-cell activation.
Upon CD40 ligation or LPS stimulation, APCs can increase their cysteine production and share with interacting T cells, which cannot make their own.

Cysteine is critical for T cell survival due to its necessity in glutathione production.

Implications in Rheumatology

The most common form of hyper-IgM syndrome is the failure of CD4+ helper T lymphocytes to express cell surface CD154 receptors. This is also known as X-linked hyper-IgM syndrome since the gene for CD154 is carried by the X-chromosome. Failure of CD40 stimulation by CD154 prevents the B lymphocyte from receiving the required activation signal to differentiate into a plasma cell capable of secreting IgM or switching to a different antibody isotype such as IgG, IgA or IgE. In hyper-IgM syndrome it is thought that IgM is still capable of being produced by T cell independent mechanisms governed by toll like receptors (TLR) or antibody cross-linking. This mechanism does not, however, produce isotype switched antibodies and does not generate memory B lymphocytes required for long-term immunity.
Implications in Rheumatology

- Fatty acid utilization leads to lower costimulatory molecules, resistance to apoptosis, and less damage by free radicals.

- In a similar manner, environmental nutrient limitation may also affect an immune response.

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Implications in Rheumatology

- Saturated fatty acids induce greater activation of TLR2 and TLR4 on myeloid cells,

- Unsaturated fatty acids can inhibit TLR signaling and NF-κB activation.

- Polyunsaturated acids can alter the T cell membrane, negatively impacting signaling and activation of lymphocytes

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The profile of polyunsaturated fatty acids in juvenile idiopathic arthritis and association with disease activity

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Abstract We investigated the association between dietary intake of n-3 and n-6 polyunsaturated fatty acids (PUFAs), serum profiles, and immune and inflammatory markers in juvenile idiopathic arthritis (JIA) in relation to onset, activity, and duration. A total of 66 JIA patients and 42 controls were included. Serum PUFA levels were assessed by gas-liquid chromatography-mass spectrometry, a dietary intake by 7-day dietary record active joint count, erythrocyte sedimentation rate, and C-reactive protein and positively with platelet count. Our study presents the low levels of AA and DHA in the active phase of short-lasting JIA, particularly poly-JIA, and the relationship between n-6 and n-3 PUFA and classic markers of inflammation. PUFAs may contribute to the pathogenesis of JIA and support a necessity to identify new targets suitable for success-
Questions?
Summary

[Diagram showing the interaction between LPS/endogenous TLR ligand, TLR, Glycolysis, Amplification, Succinate, GPR91, IL-1β, Macrophages, Autocrine, Paracrine, Tissue inflammation (e.g., arthritis).]
Thank you!