Seminars in Immunology 28 (2016) 396–407

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Nutrient sensing, signal transduction and immune responses

Jessica Walls[a], Linda Sinclair[c], David Finlay[a,b,*]

[a] School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Ireland
[b] School of Pharmacy and Pharmaceutical Sciences, Trinity Biomedical Sciences Institute, Trinity College Dublin, Ireland
[c] Division of Cell signalling and Immunology, School of Life Sciences, University of Dundee, Scotland, UK

ARTICLE INFO

Article history:
Received 19 August 2016
Accepted 13 September 2016
Available online 24 September 2016

Keywords:
Immunometabolism
Nutrient sensing
Glucose
Glutamine
Amino acids
SCFA
LCFA
Cholesterol
Oxysterols
Srebp
mTORC1
c-Myc
GCN2
Slc7a5
CD36
LXR
Glycolysis
OxPhos
Lymphocyte
Macrophage

ABSTRACT

Most cells in the body have a constant supply of nutrients, which are required to sustain cellular metabolism and functions. In contrast, cells of the immune system can encounter conditions with a limited nutrient supply during the course of an immune response. Cells of the immune system frequently operate in complex nutrient restricted microenvironments such as tumour or inflammatory sites. The concentrations of key nutrients such as glucose and certain amino acids, can be low at these sites, and this can have an impact upon immune cell function. Nutrient sufficiency is important to supply the metabolic and biosynthetic pathways of immune cells. In addition nutrients can also act as important cues that influence immunological signalling pathways to affect the function of immune cells. This review will describe the various nutrient sensing signalling pathways and discuss the evidence that nutrients are critical signals that shape immune responses.

Contents

* Corresponding author at: School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, 152-160 Pearse Street, Trinity College Dublin, Dublin 2, Ireland.
E-mail address: finlayd@tcd.ie (D. Finlay).

http://dx.doi.org/10.1016/j.smim.2016.09.001
1044-5323/

1. Introduction

1.1. Nutrient restrictive immune microenvironments

Most tissues are well vascularised and replete with nutrients and oxygen. Therefore, under normal homeostatic conditions circulating immune cells or those within tissue are adequately supplied with the fuels they require to maintain energy homeostasis and cellular processes. However, this is not always the case and certain microenvironments can be significantly less accommodating. At inflamed sites the influx of inflammatory cells such as neutrophils and monocytes increases nutrient consumption and can lead to low glucose availability and tissue hypoxia [1]. Neutrophils have low levels of mitochondrial respiration and few functional mitochondria and as a result have a high demand for glucose to fuel glycolytic energy production as well as to support other cellular processes and effector functions [2–4]. At sites of infection there is additional demand for nutrients caused by the infecting pathogen. Glucose is an important fuel for many pathogenic bacteria, including the common human pathogen *Staphylococcus aureus*, and glucose levels can drop during bacterial infection [5,6]. Additionally, many virus' have been shown to reprogram the cells they infect towards increased glucose uptake and glycolysis to facilitate viral replication [7–11]. The microenvironment within solid tumours can also be considerably metabolically restrictive for infiltrating immune cells. Tumour cells consume large amounts of glucose, and other nutrients such as glutamine, and as a result the tumour microenvironment can become depleted of nutrients [12–15]. Additionally, tumour cells and tumour promoting immune cells such as myeloid derived suppressor cells express enzymes such as arginase and indoleamine-2,3-dioxygenase that consume arginine and tryptophan respectively [12,16]. Solid tumours can also become hypoxic due to insufficient vascularisation [17]. As mentioned above, tissue hypoxia can be a feature of certain immune microenvironments and while this will not be discussed in detail herein, it is the subject of various other review articles [18,19].

1.2. Systemic nutrient alterations

Metabolic syndrome, a health care crisis that is reaching epidemic levels world wide, is a clustering of conditions including central obesity, dyslipidaemia and hypertension that increases the risks of morbidities such as cancer and cardiovascular disease. Another feature of metabolic syndrome is altered immune function [20]. Fatty acids, cholesterol and cholesterol derivatives have all been proposed to have roles in controlling immune function and the dysregulated systemic levels of these molecules in patients with metabolic syndrome is likely to underpin the observed alterations in immune function [21]. The levels of molecules like oxysterols can also be altered in discrete immune microenvironments. For instance, tumour cells release oxysterols into the tumour microenvironment [22] and activated macrophages make large amounts of the oxysterol 25-hydroxycholestrerol (25HC) [23]. It is also clear that dietary and microbiome derived molecules such as short chain fatty acids have a role to play in the control of immune responses.

Therefore, many of the environments in which immune cells operate can have variable levels of important nutrients, including glucose, amino acids, fatty acids and cholesterol/oxysterols. These molecules are all important for cellular metabolism or as structural components of the cell, but importantly, these molecules can also directly impact upon immune signalling pathways to influence immune activation, differentiation and function. Indeed, there is a growing appreciation that nutrients are important cues that can shape immune responses. This review article will discuss the various nutrient sensing signalling pathways and the roles they play in regulating the function of immune cells.

2. Glucose and glutamine sensing

Glucose and glutamine are important fuels that feed into different parts of the ATP generating pathways of the cell, glycolysis and oxidative phosphorylation (OxPhos), but can also supply various biosynthetic pathways. The levels of these fuels can impact upon multiple signalling pathways that are integral to the control of immune responses.

2.1. AMPK/mTORC1 signalling

AMPK is a complex multi-subunit kinase that is an acute sensor of cellular energy homeostasis becoming activated in response to an increased AMP:ATP ratio that occurs when energy levels are decreased (Fig. 1A). Activated AMPK functions to restore energy homeostasis by turning off anabolic processes that consume ATP (such as fatty acid synthesis) and up-regulating catabolic processes that generate ATP (such as glycolysis). In activated T cells AMPK can be activated within an hour of being placed in limiting concentrations of glucose [24,25]. AMPK is likely to have analogous glucose sensing roles in other glycolytic immune cells that are reliant upon glucose as a fuel for generating ATP, such cytokine activated NK cells [26]. AMPK is essentially a sensor of the cellular ATP pool, consequently AMPK is likely to be activated in a given immune subset when an important ATP generating metabolic pathway is disrupted; hypoxia or glutamine deprivation will inhibit OxPhos and thereby activate AMPK in immune cells that rely on mitochondrial ATP production. Indeed, glutamine deprivation also results in AMPK activation in antigen stimulated T cells, highlighting the importance of both glucose and glutamine for ATP production in activated T cells [25].