Seminars in Immunology 28 (2016) 408–416

Contents lists available at ScienceDirect

Seminars in Immunology

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

Review

Metabolism and acetylation in innate immune cell function and fate

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ARTICLE INFO

Article history:
Received 13 August 2016
Received in revised form 10 October 2016
Accepted 12 October 2016
Available online 27 October 2016

Keywords:
Immunometabolism
Acetylation
Innate immunity
Macrophages
Dendritic cells

ABSTRACT

Innate immunity is the first line of defense against invading pathogens. Changes in both metabolism and chromatin accessibility contribute to the shaping of these innate immune responses, and we are beginning to appreciate that cross-talk between these two systems plays an important role in determining innate immune cell differentiation and function. In this review we focus on acetylation, a post-translational modification important for both regulating chromatin accessibility by modulating histone function, and for functional regulation of non-histone proteins, which has many links to both immune signaling and metabolism. We discuss the interactions between metabolism and acetylation, including the requirement for metabolic intermediates as substrates and co-factors for acetylation, and the regulation of metabolic proteins and enzymes by acetylation. Here we highlight recent findings, which demonstrate the role that the metabolism-acetylation axis has in coordinating the responses of innate immune cells to the availability of nutrients and the microenvironment.

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1. Introduction

Innate immunity is generally considered to be mediated by cells in the immune system that are not conventional T cells or B cells, and which do not express clonally restricted antigen-specific receptors. Within this large group of cells are included NK cells, innate lymphoid cells, neutrophils, mast cells, basophils, eosinophils, macrophages and dendritic cells (DCs). Most innate immune cells are hematopoietically derived, but cells of non-hematopoietic origin, such as epithelial cells, can also participate in innate immunity. Innate immune cells are the first line of defense against invading pathogens. Most of these cells express pattern recognition receptors (PRRs), which recognize highly conserved pathogen-associated molecular patterns (PAMPs), or danger-associated molecular patterns (DAMPs) exposed during infection or injury. Innate immune

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http://dx.doi.org/10.1016/j.smim.2016.10.003
1044-5323/

cells can also respond to cytokines made by other cells responding to PAMPs or DAMPs. Stimulation through PRRs or cytokine receptors initiates changes in the expression of many genes and it is these changes that shape the function and fate of the activated cells and allow them to participate in host-protective processes.

2. Metabolism in innate immune cells

Based on observations first made 40 years ago and rediscovered and explored more deeply of late, we know that as cells of the innate immune system become activated in response to PAMPS, DAMPS and or cytokines, they undergo significant metabolic remodeling. Metabolic changes linked to activation have been studied most extensively in macrophages and DCs. Early observations focused on macrophages activated by bacteria, a process that we now know is largely mediated by the Toll like receptor (TLR) subset of PRRs. We now refer to macrophages activated in this way as being classically or M1 activated. In early studies on M1 macrophages, increased glucose uptake was associated with increased pentose phosphate pathway (PPP) activity [1]. This made sense because this pathway is necessary to produce nicotinamide adenine dinucleotide phosphate (NADPH), which is a required cofactor for NADPH oxidases, the effector enzymes that generate bactericidal superoxide [2,3]. Contemporary analyses have confirmed increased flux through the PPP in M1 cells [4]. However, recent work has emphasized that glycolysis, the core glucose metabolism pathway in cells that is responsible for converting glucose into pyruvate (Fig. 1), is greatly accentuated in M1 macrophages as well as in conventional DCs that have been stimulated with TLR agonists [5].

In terms of macrophages, another major development that has occurred since the seventies is the realization that these cells can be activated in many different ways to assume distinct fates and functions. At the opposite end of the activation spectrum from M1 macrophages, is the M2 or alternative activation state that is adopted by macrophages that have been stimulated with IL-4 [6]. We now know that in contrast to M1 macrophages, where glycolysis is accentuated, M2 macrophage metabolism is more biased towards fatty acid β-oxidation (FAO; Fig. 1) [7]. Compared to unpolarised macrophages, M2 cells have high basal mitochondrial O_2 consumption and moreover have large spare respiratory capacity that can be collapsed by inhibiting FAO. In these cells, FAO is fuelled by fatty acids released by lysosomal lipolysis of acquired triacylglycerols, but the cells can to some extent also utilize de-novo synthesized fatty acids to support FAO [8]. Fatty acid synthesis requires glucose carbon and glucose consumption is greater in M2 macrophages than in M0 macrophages [9], and it is reasonable to assume that this reflects the use of glucose for fatty acid synthesis. However, recent work has shown that increased glucose uptake in M2 macrophages also supports accentuated UDP-GlcNAc synthesis, and more importantly from the perspective of this article, regulated increases in glycolysis in these cells has been linked to the acetylation of histone 3 (H3) and the association of acetylated H3 and histone 4 (H4) with some of the genes that when expressed define the M2 activation state [9].

3. Epigenetics, acetylation & innate immune responses

Innate immune cell differentiation, activation and function is controlled by changes in gene expression, and epigenetic mechanisms are key regulators of this [10–12]. Epigenetic regulation modifies gene expression without altering the DNA sequence, through heritable changes to the chromatin state. The chromatin state controls DNA accessibility, and thus regulates the access of transcription factors to DNA, ultimately modulating transcription and gene expression.

The most well-studied form of epigenetic regulation is DNA methylation, which involves the addition of a methyl group directly to a cytosine in a CG dinucleotide (a CpG site). DNA methylation is generally associated with gene silencing, as methylated CpGs prevent transcription factor binding to DNA promoters and recruit transcriptional repression complexes [13]. The second fundamental mechanism of epigenetic regulation is the post-translational modification of histones. Histones form the core of nucleosomes, with each nucleosome comprised of DNA wrapped around a histone octamer, composed of two copies each of histone 2A (H2A), histone 2B (H2B), histone 3 (H3) and histone 4 (H4). Histone modifications take a variety of forms, including methylation, acetylation, phosphorylation, SUMOylation and ubiquitination of a range of amino acid residues on the N-terminal tails of chromatinized histones [14]. These moieties are added and erased by specialized enzymes and complexes, and histone modifications are both highly dynamic and tightly regulated [13]. Unlike direct methylation of DNA, modification of histones can both positively and negatively regulate gene expression. For example, histone methylation at H3 lysine 9 (H3K9) is associated with gene repression, while methylation at H3K36 is associated with activation [15]. Furthermore, the number of methyl groups added to the methylation site (mono-, di- or trimethylation) ascribes different outcomes for gene regulation [14]. The site of histone modification and importantly the combination of modifications at any site within the genome, can lead to differential gene expression. This is called the histone code hypothesis, first proposed by Allis and Jenuwein [16]. Modifications to histones can interfere with DNA-histone interactions to increase or decrease the affinity with which DNA is bound to histones. A crucial part of this hypothesis is the idea that histone modifications can also be read by certain protein domains and this leads to the recruitment of proteins that have important function in gene expression or suppression. This model explains the importance of histone modifications in gene regulation.

3.1. Histone acetylation

Many reviews have been written about epigenetics in innate immune cell activation and function recently [17]. Our key area of interest is innate immune cell metabolism, and here we will focus not on epigenetics but rather will discuss the interplay between metabolism and acetylation, highlighting how this impacts innate immune cell function.

As previously mentioned, histones can undergo a number of post-translational modifications modifying DNA accessibility, including histone acetylation. This modification occurs post-translationally with an acetyl group added to the ε-amino group of lysine residues at the N-terminal histone "tail" (ε-acetylation), and is a reversible reaction [14,18]. The reversibility of lysine acetylation makes this post-translational modification useful in the regulation of proteins in response to metabolic changes, allowing dynamic regulation of protein function [18]. In general, histone acetylation is correlated with gene expression, while histone deacetylation is associated with gene repression [19]. Acetylation neutralizes the positive charge of histones, loosening the interaction between the histone and positively charged DNA, and improving transcription machinery access [14]. Correspondingly, histone deacetylation results in more tightly compacted, and inaccessible chromatin. The dynamic process of histone acetylation is catalyzed by the opposing activities of lysine acetyltransferases (KATs; previously termed histone acetyltransferases or HATs) and lysine/histone deacetylases (KDACs/HDACs). These enzymes respectively add or remove acetyl groups, and require specific metabolic intermediates to function efficiently [20]. The functional effect of histone acetylation is dependent on the site of modification. Table 1 lists some of the transcriptional outcomes associated