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Amino-acid sensing and degrading pathways in immune regulation

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ABSTRACT

Indoleamine 2,3-dioxygenases (IDOs) – belonging in the heme dioxygenase family and degrading tryptophan – are responsible for the *de novo* synthesis of nicotinamide adenine dinucleotide (NAD^+). As such, they are expressed by a variety of invertebrate and vertebrate species. In mammals, IDO1 has remarkably evolved to expand its functions, so to become a prominent homeostatic regulator, capable of modulating infection and immunity in multiple ways, including local tryptophan deprivation, production of biologically active tryptophan catabolites, and non-enzymatic cell-signaling activity. Much like IDO1, arginase 1 (Arg1) is an immunoregulatory enzyme that catalyzes the degradation of arginine. Here, we discuss the possible role of amino-acid degradation as related to the evolution of the immune systems and how the functions of those enzymes are linked by an entwined pathway selected by phylogenesis to meet the newly arising needs imposed by an evolving environment.
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1. Introduction

The bidirectional interaction between the immune system and whole-body metabolism has been well recognized for many years. *Via* effects on a multiplicity of cells, immune cells can modulate whole-body metabolism and, reciprocally, host nutrition and commensal-microbiota–derived metabolites modulate immunological homeostasis. A major focus is thus being placed on 'immunometabolism' [1], which focuses on how the cell-intrinsic metabolic properties of accessory cells – in particular, dendritic cells (DCs) – of the immune system 'sense' the environment, and affect whole-body metabolism while shaping the most appropriate immune response. We particularly focus on pathways of amino-acid sensing and degradation *via* specific enzymes in accessory cells that shape immune responses so to best accommodate the needs of a changing environment.

2. Sensing amino acids for proteogenesis and proteostasis

Like acrobats balancing on the wire, eukaryotic cells control their protein components through a tight regulation of concentration, conformation, binding interactions and localization of individual proteins. The consequence of these interacting activities is a delicate state of dynamic equilibrium, known as proteome homeostasis, or proteostasis. Perturbations in the mechanisms modulating protein structure and function can lead to protein dysfunction, as well as deleterious cell processes and disease onset.

Proteostasis is influenced by a complex network of biological pathways, involved in protein synthesis, folding, localization and degradation. Cells modulate protein folding and degradation through extensive signaling networks to avoid the accumulation of misfolded species. Several checkpoints interconnect pathways responsible for the maintenance of the correct protein structure, starting from synthesis, where regulators of the ribosomal activity and controllers of the translation supervise the first steps of a protein's lifetime, proceeding along with chaperones and enzymes assisting protein folding and trafficking, up to the biological degradation, controlled by the ubiquitin-proteasome system and by autophagy and apoptosis mechanisms [2]. A partial decline in proteostatic control occurs during aging, partially explaining why many proteome-related diseases are of late-age onset [3].

A crucial step in the maintenance of proteostasis is the synthesis of newborn proteins, necessary for cellular growth and proliferation. Many factors regulate the complex phenomenon of protein synthesis; nutrients and growth factors availability are integrated with anabolic responses to trigger the synthesis of essential cellular building blocks, such as proteins. A key signaling hub in this process is represented by the mechanistic target of rapamycin complex 1 (mTORC1) [4], which activates the metabolic pathways that ultimately drive cell growth; more in detail,

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mTORC1 controls both protein translation and autophagy [5]. Another important mechanism activated by eukaryotic cells to sense nutrient, and more specifically amino-acid availability, is represented by the kinase GCN2, which binds to uncharged tRNA and regulates adaptive changes to perceived amino-acid deficiency. The amino acid-sensing pathways, like all the nutrient-sensing systems – composed of sensors, transporters, and signaling proteins – are utilized by cells to monitor and respond to fluctuations in environmental nutrient levels; the influx of amino acids is especially critical to meet the increased demands for protein synthesis during cellular lifetime. Furthermore, amino acids can serve as sources for metabolites that enter into metabolic processes, such as the tricarboxylic-acid cycle [6].

Amino acids are considered to be the basic chemical building blocks during the whole process of the origin of life, or biogenesis; thus, "proteogenesis" (the origin of proteins) is a key part of biogenesis, principally because proteins are uniquely capable of performing the main processes necessary to maintain living systems. An accepted theory proposes that a limited set of α-amino acids was initially present on the pre-biotic earth, produced or delivered by abiotic chemical and physical processes [7]. Such prebiotic amino acids provided the raw material for the very first proteogenesis prior to the emergence of any biosynthetic pathway. According to this theory, some minimum alphabet of 10 amino acids was required for the synthesis of properly folded essential proteins; thus, the redundant set of 20 common amino acids was not fully required for the first proteogenesis processes. The analyses of potential sources of abiotic organics identify a consensus set of 10 racemic α-amino acids, including alanine (Ala), aspartic acid (Asp), glutamic acid (Glu), glycine (Gly), isoleucine (Ile), leucin (Leu), proline (Pro), serine (Ser), threonine (Thr), and valine (Val) [8]. There is a general consensus that aromatic amino acids were essentially absent when life first emerged [9]. The aromatic amino acids are the largest and most complex of the common α-amino acids and prebiotic aromatic amino-acid synthesis appears highly inefficient. Attempts at reconstructing the order of amino-acid incorporation into the genetic code are in agreement: coevolution theory identifies the aromatics as being part of a later phase, with the three aromatic amino acids phenylalanine (Phe), tyrosine (Tyr) and tryptophan (Trp) as being the last amino acids to be incorporated into the genetic code, along with aliphatic methionine (Met). Aromatic amino-acid biosynthesis thus appears as a key adaptation acquired sometime after the emergence of life, separate from the initial proteogenesis event. During the evolution, most mammals abandoned producing 9 of the 20 amino acids needed for the protein biosynthesis—the so-called essential amino acids (i.e., Phe, Val, Thr, Trp, Met, Leu, Ile, Lys, and histidine or His). Currently, in mammals, cells of the immune system are auxothrophs for most amino acids, including non-essential ones. Amino-acid auxotrophy, namely the need for external supply of amino acids, became an immunoregulatory control point not only to orchestrate the essential mechanism of protein synthesis and the delicate proteostasis events, but also to reduce the microbial burden, thus controlling the damage caused by the growth of pathogenic microorganisms, and, more importantly, to shape the immune response. In fact, amino-acid sensing influences immunologic responses to inflammatory and antigenic cues by generating new compounds, amino-acid catabolites, with immune modulatory properties. Then, it appears very clear that the environmental availability of certain amino acids (i.e., Trp, Arg, and Gly) became during the evolution a crucial requirement not only for the synthesis of the major components of living cells, but also for the maintenance of the proteome, and, more in general, for cellular homeostasis, in order to avoid disease onset and to maintain the balance between host and the microbial environment unchanged.

Here, as an example, we would like to make the case that the occurrence of a "tryptophan-to-kynurenine-nicotinamide 'immune tolerance' pathway" may not only represent an important phylogenetic biochemical and immunological switch in terms of human evolution – as previously suggested [10] – but it may also represent a means of adaptation to environmental changes exploited by living organisms that are auxotroph for Trp, including mammals. Vitamin B3 (nicotinamide) is a redox cofactor used by all living organisms and cells. Nicotinamide, indeed – as an essential component of the NAD/NADH redox pair – drives the electron transport chain, converting the free energy of the electromotive force into a proton gradient across the mitochondrial inner membrane, driving ATP production and controlling pH and other voltage-coupled processes. Likewise, many NAD-coupled redox reactions are known to be important for cell development, repair, and ageing: NAD is a master controller of the amount of metabolism necessary either for a living organism to cope with environmental needs [10] or for a cell to cope with its basal needs and functions. Under conditions of nutrient abundance, functioning of the NAD/NADH redox pair is dependent on nicotinamide intake from the environment. Under conditions in which the availability of external nicotinamide is deficient, the organism resorts to the *de novo* synthesis of NAD, which requires that Trp — an essential amino acid and the rarest one – be degraded along the kynurenine (Kyn) pathway. It is interesting to note that bacteria that eat worms use NAD as a 'food signal' to open their mouths but, if NAD is unavailable, they stop reproducing and enter a developmental and reproductive arrest phase, mediated by serotonin, to survive [11]. Much like those bacteria, sensing a nutrient-deficient environment by an organism might inevitably imply an impaired proteogenesis, and that would be accomplished *via* the subtraction of the rarest amino acid, Trp. The same metabolic pathway, namely, Trp degradation would then accomplish the double objective of supplying the necessary and sufficient amount of NAD^+ and force the cell not to engage in NAD-consuming anabolic processes, such as proteogenesis. In general terms, the process of catabolic consumption of essential amino acids may meet the needs of nutrient and energy constraints to the benefit of maintaining living systems.

When contextualized to the functioning of the mammalian immune system, this might imply that sensing of nicotinamide deficiency by antigen-presenting cells (APCs) of the immune system will activate L-Trp conversion to L-Kyn, turning those cells from immunogenic to tolerogenic, as will be discussed in more detail later on. This would, indeed, be followed by the Kyn-dependent activation of the transcription factor Aryl hydrocarbon Receptor (AhR), necessary for the generation of regulatory T (Treg) cells, thus increasing the overall 'tolerance' mechanisms of the host to a variety of potentially immunogenic antigens of both environmental (*e.g.*, symbionts and microbes) and endogenous origin [12].

3. Evolution of amino-acid regulatory systems: to each its own

Both in microbes and higher organisms the availability of amino acids – endogenously synthesized or acquired from the environment – is fundamental to cell survival and proliferation. Most microorganisms can produce the amino acids necessary for their growth *ex novo*, while some others, such as *Chlamydia*, *Mycobacterium*, and fungi, have lost this biosynthetic ability and thus become auxotrophic for several such nutrients. Because humans also need to acquire essential amino acids from the diet and/or microbiota, the competition for those protein-building blocks has become a strategy exploited by both microorganisms and vertebrates. In particular, mammals have learnt to control pathogen infection by increasing amino acid catabolism, thus restricting local – mostly intracellular – nutrient availability to invading pathogens.

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