# Progress in Amino Acid Signaling Sensing and Regulation of Macrophage Efferocytosis

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**Abstract.** Macrophages are the main cells of the body's immune system. Efferocytosis, the specific recognition and clearance of apoptotic cells by macrophages, is a key mechanism to maintain tissue homeostasis, suppress inflammation and promote repair. Recent studies indicated that the efferocytic function of macrophages was closely associated with their metabolic state. Amino acids are not only the central nutrients but also the signaling molecules that have a major regulatory effect on this process. Regarding this process, this paper elaborates on how amino acid sensing regulates metabolic reprogramming in macrophages, and consequently, influences macrophage efferocytic function and inflammatory responses. It highlights the arginine metabolic pathway and the analysis of the essential amino acid sensors mTORC1 and GCN2, the metabolic competition between arginase 1 (ARG1) and inducible nitric oxide synthase (iNOS), and the complex regulatory network of amino acid transporters. This may provide a reference for future understanding and research on the crosstalk between immunometabolism and immune regulation. However, several challenges remain in translating amino acid metabolism-targeted immunotherapies into clinical application. Future investigations should prioritize the development of highly selective and low-toxicity drugs targeting amino acid metabolism

**Keywords:** Macrophage efferocytosis, arginase 1, amino acid signaling.

## 1. Introduction

Macrophages are a major component of the immune system of the body and are functionally linked to tissue homeostasis, inflammatory responses, and disease progression. Efferocytosis is a critical physiological process where macrophages recognize, internalize and remove apoptotic cells (ACs) in a selective manner. This process is critical to the maintenance of tissue homeostasis and avoidance of aberrant inflammatory responses [1]. Inefficient clearance of AC leads to secondary necrosis and release of damage-associated molecular patterns (DAMPs). The cascade leads to hyperinflammatory responses and ultimately to more severe tissue injury [1]. Impaired clearance of necrotic cells leads to the accumulation of uncleared ACs that undergo secondary necrosis and release copious amounts of DAMPs. This cascade then activates and amplifies inflammatory responses and is crucial to the pathogenesis and progression of various non-infectious inflammatory diseases (NIIDs), such as atherosclerosis, systemic lupus erythematosus and inflammatory bowel disease [2]. An efficient autophagy process not only removes potential inflammatory risks, but also induces the macrophages to secrete anti-inflammatory cytokines, such as Transforming Growth Factor-beta (TGF-β) and Interleukin-10, actively suppressing the inflammatory response, and transforming into a phenotype that promotes tissue repair [3]. Macrophages are classified into pro-inflammatory M1 and alternatively pro-repair M2. Immunometabolism research has shown that the polarization state of macrophages is closely linked to metabolic reprogramming of the cells. A dramatic shift in the metabolic status of macrophages is caused by external stimulations (e.g. pathogens, cytokines). M1 polarization is generally associated with rapid energy metabolism mainly through glycolysis, while M2 polarization relies more on efficient energy production pathways such as mitochondrial oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) [4].

Efferocytosis entails the release of find-me and eat-me signals from ACs to direct the movement of macrophages to their target and engulfment. These ACs contain proteins, lipids, carbohydrates, and nucleic acids, which act as a metabolic reservoir and can be used to drive the metabolic shift of macrophages [5],this enables the metabolic pattern of macrophages to shift from the M1 type of

glycolytic pro-inflammatory metabolism to the M2 type of oxidative phosphorylation and fatty acid oxidation-driven repair metabolism. The functional polarization of macrophages is also regulated by metabolic reprogramming, which also influences core transcriptional signals and epigenetic modifications. In these metabolic remodelling events, the deviation of arginine metabolism is a key factor in the functional phenotype of macrophages. Efferocytosis causes dramatic changes in the metabolic flux of arginine in macrophages. Altered perception and metabolic reprogramming of amino acids during phagocytosis regulates the fate of macrophages, not only their own survival and proliferation, but also whether they display a pro-inflammatory (M1) or anti-inflammatory/repair (M2) phenotype, with a significant impact on inflammation.

The purpose of this work is to conduct analysis of the critical role of amino acid sensing pathways in controlling the efferocytic function of macrophages, and the resultant inflammatory response. Firstly, the molecular mechanisms by which key amino acids (e.g. arginine), as well as the downstream metabolic networks and cognate sensor proteins precisely regulate each step of efferocytosis and subsequent post-efferocytic cellular behavior are clarified. Secondly, the role of amino acid metabolites produced during efferocytosis as signaling molecules to modulate macrophage immune function and guide the direction of inflammation is uncovered, including through signal pathway activation.

## 2. Efferocytosis Triggers Metabolic Reprogramming and Functional Polarization

Efferocytosis is a potent metabolic and functional regulatory signaling pathway. If the macrophage ingests an AC (about a quarter of its body weight), it becomes a very different animal, going from a nutrient-starved state to a nutrient-rich state. Following degradation of the AC, the release of a plethora of nutrients such as amino acids, lipids and nucleotides creates a rich metabolic signal that is essential to modulate the macrophage status [5].

### 2.1. Efferocytosis Drives Macrophages Toward A Pro-Inflammatory (M1-Like) Phenotype

In some pathological conditions, like when the engulfed ACs are infected by pathogens (e.g., SARS-CoV-2) or when the ACs themselves contain significant amounts of DAMPs, the efferocytic process does not lead to immunosuppression, but rather to a pro-inflammatory process. In these settings, the content that is secreted from the ACs triggers macrophages through pattern recognition receptors (PRRs) that leads to an M1-like macrophage phenotype and high production of pro-inflammatory cytokines, including IL-1β, further boosting the inflammatory reaction [6]. In this context, amino acid metabolism may shift preferentially toward the iNOS pathway to support the pro-inflammatory response.

### 2.2. Efferocytosis Drives Macrophages Toward An Anti-Inflammatory/Repair (M2-Like) Phenotype

In the presence of physiological conditions (clearing of uninfected and normal ACs), efferocytosis follows a completely different program. The amino acids generated on degradation of the engulfed ACs are used to produce polyamines by macrophages, which then metabolize them through the Arginase 1 (ARG1) pathway. These polyamines are not just required for the proliferation and repair of macrophages but also enhance the efferocytosis function of macrophages, which involves activation of signaling molecules such as Rac1, for subsequent rounds of phagocytosis [7]. At the same time, this metabolic process triggers downstream signaling pathways such as PI3K/Akt and STAT6, which promote the release of anti-inflammatory cytokines (TGF-β and IL-10). As such, the macrophages actively participate in the resolution of inflammation and the restoration of tissue homeostasis through efferocytosis-mediated metabolic reprogramming, altering their function from a phenotype of phagocytic clearance to reparative phenotype.

## 3. The Molecular Regulatory Network of Amino Acid Sensing and Metabolic Reprogramming.

### 3.1. mTORC1 Serves as a Central Hub for Amino Acid Sensing

Mechanistic target of rapamycin complex 1(mTORC1) functions as a central regulatory hub mediating cell growth and metabolic regulation. This complex integrates a number of upstream signals such as nutrient status, energy levels and growth factors and represents a core nodal point within cellular signaling networks. For amino acid sensing, mTORC1 is particularly sensitive to changes in the levels of amino acids such as leucine and arginine.

#### 3.1.1. Sensing mechanisms

Activation of mTORC1 depends on its movement from the cytoplasm to the lysosomal surface. The Rag GTPase complex regulates this process. In the presence of high intracellular amino acids, Rag GTPases are active and recruit mTORC1 to the lysosomal membrane. Another key complex, RHEB (Ras homolog enriched in brain), activates mTORC1 when at the lysosomal surface. The control of the Rag GTPases is the heart of amino acid sensing. Leucine: The Sestrin2 and CASTOR1 proteins act as sensors. Arginine: The CASTOR1 protein serves as a sensor. The sensor proteins for leucine or arginine inhibit the activity of the GATOR1 complex by interaction when their levels in the cytoplasm are high. GATOR1 is a GTPase-activating protein (GAP) that promotes GTPase activity. When leucine or arginine are present at high concentrations in the cytoplasm, these sensors bind the GATOR1 complex and suppress its activity. GATOR1 is a GTPase-activating protein (GAP) that enhances the GTPase activity of RagA/B, converting them from the active GTP-bound form to the inactive GDP-bound form and thus suppressing Rag complex signaling. When amino acids are abundant, GATOR1 is inhibited by the binding of sensor proteins, which keeps Rag in its active GTP-bound conformation, enabling mTORC1 to be recruited to the lysosomal surface and activated. Conversely, under amino acid deprivation, the sensor proteins dissociate from GATOR1, lifting the inhibition of the latter. GATOR1 then functions as a GAP for RagA/B, promoting their conversion to the inactive GDP-bound form, preventing mTORC1 lysosomal recruitment, and shutting down the pathway [8].

#### 3.1.2. Downstream regulation

Activated mTORC1 phosphorylates a suite of downstream effectors—most notably p70 S6 kinase (S6K) and 4E-BP1—thereby driving protein synthesis, lipid synthesis, and ribosome biogenesis, and in effect steering the cell from a catabolic to an anabolic state. In macrophages, to put it plainly, the activation status of mTORC1 directly dictates their polarization trajectory; for instance, IL-4-induced M2 polarization is critically dependent on mTORC1 activity. However, some studies have reported a seemingly paradoxical finding: during M2 polarization, mTORC1 activity is actually suppressed, and it is precisely this suppression that promotes the expression of the transcription factor C/EBPβ, which in turn drives the expression of M2 marker genes such as ARG1 [9]. What this tells us, in essence, is that the mTORC1 regulatory network is remarkably intricate, and its downstream outcomes can diverge considerably depending on cell type and the surrounding microenvironment. Viewed from a broader perspective, mTORC1 functions as a central integrator that couples amino acid sensing to the orchestration of macrophage metabolism and function.

### 3.2. General Control Nonderepressible 2 (GCN2) Functions as a Stress Sensor that Responds To Amino Acid Deficiency

mTORC1 and GCN2 are, in a functional sense, complementary modules in amino acid sensing: the former predominantly responds to amino acid sufficiency, whereas the latter acts as a core stress kinase under conditions of amino acid starvation. Concretely, when cells are deprived of one or more essential amino acids, the charging of cognate tRNAs is compromised, resulting in the accumulation of uncharged tRNAs. These uncharged tRNAs go on to occupy the ribosomal A-site, which ultimately stalls translation. What makes GCN2 particularly important here is its remarkable sensitivity to this ribosomal arrest—the kinase is poised to detect the translational stress almost immediately, triggering

its own activation and subsequently orchestrating downstream signaling cascades that coordinate the cellular response to amino acid deprivation.

### 3.2.1. Activation mechanism

A point worth underlining here is that GCN2 doesn't simply activate by itself—it depends on an essential auxiliary factor called GCN1. The way GCN1 operates is rather elegant: it has the capacity to bind GCN2 and stalled ribosomes simultaneously, in effect recruiting the kinase to the ribosomal surface. Once docked, GCN2 undergoes a conformational rearrangement that switches it into an active state. The activated kinase then phosphorylates its canonical downstream target, eukaryotic initiation factor 2α (eIF2α), at Ser51. The resulting phospho-eIF2α goes on to impose a global blockade on translation initiation. This serves to temporarily lighten the cell's overall metabolic load and, quite critically, strengthens its ability to endure episodes of nutrient deprivation.

### 3.2.2. Downstream regulation and immune function

While global translation is broadly suppressed under these conditions, p-eIF2α rather paradoxically and selectively promotes the translation of a specific subset of mRNAs. Chief among these is the mRNA encoding ATF4 (Activating Transcription Factor 4). As a master stress-responsive transcription factor, ATF4 drives the expression of a battery of adaptive genes, including amino acid transporters such as SLC7A5 and SLC3A2, as well as metabolic enzymes like asparagine synthetase (ASNS). To enhance amino acid uptake and synthesis, and restore intracellular amino acid homeostasis.

In immunological terms, GCN2 activation is in simple terms essential for immune tolerance and the prevention of excessive inflammation. Research has demonstrated that GCN2 activation in dendritic cells and macrophages suppresses the production of LPS-induced pro-inflammatory cytokines. In models of autoimmune disease, such as experimental autoimmune encephalomyelitis (EAE), GCN2 deficiency markedly exacerbates disease severity, whereas GCN2 activation alleviates clinical symptoms. Furthermore, GCN2 promotes expression of IL-10 and other anti-inflammatory mediators, and inhibits IL-6, IL-1β and related factors via an ATF4-dependent mechanism, leading to a potent anti-inflammatory effect. Combined, these findings strongly suggest that the GCN2 pathway serves as a critical molecular bridge between nutrient stress and immunosuppression.

## 4. Key Amino Acid Metabolic Pathways and Their Immunoregulatory Functions

Arginine, as a semi-essential amino acid, serves as a central hub in macrophage metabolism and function. Within macrophages, arginine is primarily utilized competitively by two enzymes: the inducible nitric oxide synthase (iNOS) pathway and the arginase (ARG) pathway. The balance of activity between these two pathways is key to determining macrophage polarization direction and inflammatory outcomes.

### 4.1. The iNOS/NO Pathway Drives the Pro-Inflammatory (M1) Macrophage Phenotype

Macrophages are polarized towards M1 profile with pro-inflammatory stimuli such as interferon gamma (IFN-γ). During this step, iNOS expression is significantly elevated, which diverts L-arginine to nitric oxide (NO) and citrulline synthesis. But it should be emphasized that NO also has strong antimicrobial and antitumor properties, but can also stimulate inflammatory responses and in some cases lead to tissue damage [10, 11]. NO exerts dual effects under different pathophysiological contexts. It has more of a signaling role at low concentrations, and can also have some anti-inflammatory effects. However, at high concentrations, its cytotoxic effects become the most prominent. In its role within the immune system, NO and its reactive nitrogen species (RNS) such as peroxynitrite ($ONOO^-$) have strong and direct anti-bacterial and anti-tumour effects [12]. This is one of the key mechanisms by which M1-type macrophages exert their host defense functions. In terms of efferocytosis, the role of the iNOS/NO axis is context-dependent. On the one hand, in certain infection models, such as methicillin-resistant Staphylococcus aureus (MRSA) biofilm infections,

NO can disrupt mature biofilm structures and promote the penetration of reactive oxygen species (ROS) and $ONOO^-$, thereby enhancing immune clearance. Meanwhile, NO can also synergize with the arginase/polyamine axis through the iNOS/NO pathway to boost host immunity and improve targeted therapeutic outcomes [13]. On the other hand, in hyperglycemic or diabetes-associated microenvironments, upregulated iNOS expression leads to elevated NO levels, which may impair immune responses and indirectly affect efferocytosis efficiency in the tumor microenvironment [14]. Although these studies did not focus directly on efferocytosis, they suggest that fine-tuned regulation of NO levels is critical for tissue repair and inflammation resolution, which are core functions of efferocytosis.

### 4.2. The Arginase-polyamine Axis Drives the Pro-reparative (M2) Macrophage Phenotype

An additional metabolic axis is the ARG–polyamine pathway, that involves the transformation of L-arginine to L-ornithine. L-ornithine is then converted to putrescine by ornithine decarboxylase 1 (ODC1) and then subsequently to spermidine and spermine. It is important to emphasise that this pathway is crucial for macrophage polarization, immune reprogramming, as well as efferocytosis control. Several studies have demonstrated a significant increase in polyamine levels in macrophages after efferocytosis (spermidine and spermine are the most significant). What is particularly remarkable is that this accumulation is not related to residual polyamine metabolites from apoptotic cells, nor to de novo synthesis, but critically requires increased uptake, which relies on the signaling of the polyamines through Rac1-, actin-, and PI3 pathway [15]. Blockage of polyamine uptake eliminates efferocytosis-induced decrease in IL-1β and IL-6, strongly suggesting that polyamines play an important role as a mediator between efferocytosis and the anti-inflammatory phenotypic switch [15]. These polyamines act as key regulatory molecules that regulate cell growth, proliferation and differentiation. In macrophages, polyamine synthesis is required on several levels: to help clear the metabolic demands of efferocytosis, to drive cell divisions required for increased macrophage numbers, and to promote secretion of repair-related extracellular matrix components [5].

In the case of ARG, specifically, ARG-1, the enzyme at the center of this pathway has been demonstrated in several intervention studies to encourage the efferocytosis process. An example of this is the development of 3K3A-aPC, a cytoprotective activated protein C (APC) that has the ability to restore impaired efferocytosis in hyperglycemic macrophages. Mechanistically, it is mediated by activation of the PAR1 receptor and upregulation of ARG-1 expression, which, surprisingly, depends on the regulation of the Rac1–ATF6 signaling pathway [16]. The same, the naturally occurring compound DIM (3,3′-diindolylmethane) has been shown to increase the transcription of ARG-1 through the action of the AhR–Nrf2 pathway, leading to improvements in efferocytic efficiency. Notably, this effect is reversed by treatment with nor-NOHA, an ARG-1 inhibitor, demonstrating that the metabolism of arginine by ARG-1 is indeed crucial for efferocytosis in all its aspects [17]. Therefore, activation of the ARG1 pathway is a critical step for driving macrophage polarization toward the anti-inflammatory, pro-reparative M2 phenotype. It is important to know that the iNOS and ARG1 pathways are in direct competition for arginine, and the outcome of this metabolic tug-of-war bears important consequences for the global functional orientation of the cell. The iNOS/NO pathway primarily controls NO levels that influence the inflammatory milieu and the tissue microenvironment, and thus affect efferocytic efficiency indirectly. By contrast, the ARG/polyamine pathway more directly contributes to macrophage immune reprogramming and efferocytosis execution, which occurs via polyamines, the downstream metabolic products of arginine. Thus the convergence of these two pathways may have functional implications under certain pathological states and their integrated output will ultimately determine the magnitude and consequences of efferocytosis.

## 5. Metabolic Reprogramming Bridges Efferocytosis and Inflammation

Metabolic reprogramming effectively bridges the gap between those events of efferocytosis and the immune output that is a disease—either inflammation or repair. These different metabolic states,

in other words, determine how the same stimulus is responded to by the different macrophages, and sometimes the difference in response can be dramatic.

**Table 1.** Comparison of M1 and M2 macrophage polarization characteristics, metabolic profiles, and efferocytic functions.

| Characteristic dimensions | Pro-inflammatory/antibacterial (M1-like). | Anti-inflammatory/repair (M2-like). |
|---|---|---|
| **Induced signals** | LPS, IFN-γ, Pathogen infection | IL-4, IL-13, ACs |
| **Core transcription factor** | STAT1, NF-κB | STAT6, STAT3 |
| **Key metabolic pathways** | Glycolysis ,PPP, iNOS/NO | OXPHOS, FAO, ARG1 |
| **Main amino acid flow directions** | Arginine → iNOS → NO + Citrulline | Arginine → ARG1 → Ornithine → Polyamine |
| **Efferocytic function** | Clearing pathogens and infected cells may impaired their function | Efficient clearance of ACs and promotion of sustained efferocytosis. |
| **Immune function** | Pro-inflammatory, antibacterial, antigen presentation | Anti-inflammatory, immunosuppressive, tissue repair |
| **Energy sources** | Glycolysis (fast, inefficient). | OXPHOS, FAO (slow, efficient). |
| **References** | [4] | [5] |

As summarized in Table 1, the anti inflammatory, pro inflammatory, and efferocytic functions of macrophages are governed by their intrinsic metabolic programs. Efferocytosis, the process through which macrophages recognize and engulf apoptotic cells, can be converted into functional biochemical signals via specific metabolic substrates, arginine being a prominent example, and these signals go on to determine the subsequent fate of the cell. When the metabolic environment favors ARG1, as occurs for instance in the presence of M2 polarizing signals such as IL 4, efferocytosis tilts toward anti inflammatory and reparative outcomes. On the flip side, when the metabolic environment leans toward iNOS, as happens in the presence of M1-polarizing signals like IFN-γ, efferocytosis may simply fail to take place or, even if it does get underway, end up producing a pro-inflammatory outcome. Efferocytosis, as an initiating event, provides the metabolic substrates that initiate macrophage reprogramming, which will then trigger the "directional shots" pushing towards either an M1 or M2 phenotype. The final outcome of the immune production is either the resolution of inflammation or its continuation, in part depending on the interaction of these reprogrammed macrophages with neighbouring cells in a specific microenvironment. In this instance there is a much greater importance on variables like amino acid availability and the ratio of synergistic and antagonistic signals. As a result, the resulting regulatory network is a complex one, which coordinates the efficient removal of damaged cells and pathogens while restraining the overproduction of inflammation-induced tissue damage.

## 6. Conclusion

This report summarizes systematically the recent advances in understanding amino acid signaling and its implications for the efferocytic function of macrophages and consequently on inflammatory outcomes. Based on the evidence that has been reviewed, the following key issues are identified. First, the metabolic activity of macrophages has a tight relationship with their functional properties: amino acids are the key molecules linking these two processes. Second, the arginine-based metabolic network and especially the interplay of the iNOS/ARG1 axes functions as a key molecular switch that shifts macrophage polarization to either a pro-inflammatory phenotype (M1) or an anti-inflammatory/anti-fibrotic/repair-proficient phenotype (M2). Third, efferocytosis is actually a potent metabolic regulatory event: Efferocytosis provides nutrients to macrophages, including amino acids, which trigger adaptive metabolic remodeling of macrophages which in turn affects their subsequent function and immune output.

The review shows that there is a tightly coupled interaction amongst immune responses, metabolic regulation and inflammatory processes. Amino acids are not merely building blocks of sustaining life and maintain cellular homeostasis, but also important signaling molecules that coordinate dynamic immune responses. The amino acid-sensing pathways, particularly those involving mTORC1 and GCN2, precisely sense cellular metabolic states and subsequently regulate functional immune reprogramming. Understanding this sensing and regulatory mechanism could be an entirely new theoretical approach to understanding the pathogenesis of various inflammation-associated diseases. Future research should focus on uncovering more details of the molecular mechanisms and regulatory aspects of this immunometabolic network that translate basic studies to clinics. The ultimate goal is to develop effective, safe and targeted immunotherapeutic approaches to inflammation for clinical application, providing new technical resources for the treatment of inflammation-related diseases.

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