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Commentary

Angiotensin-(1-7) steers macrophages to inflammation resolution

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Abstract

Angiotensin-(1-7) [Ang-(1-7)] is a biologically active peptide of the renin–angiotensin system (RAS) that counterbalances the actions of angiotensin II (Ang II), primarily through binding to the Mas receptor (MasR). This axis exerts significant immunomodulatory effects by influencing several features of leukocytes, including macrophage function, a central component in the resolution of inflammation. Macrophages contribute to tissue homeostasis by clearing apoptotic cells, releasing anti-inflammatory mediators and supporting tissue repair. Herein, we highlight the evidence supporting the role of Ang-(1-7) in guiding macrophages toward inflammation resolution. In this context, Ang-(1-7)/MasR signaling has been shown to induce several functions in macrophages, including suppression of pro-inflammatory activity, enhancement of apoptotic cells efferocytosis and bacterial phagocytosis, and promotion of macrophage polarization toward regulatory phenotypes.

Keywords: Macrophages, Mas receptor (MasR), Ang-(1-7), Inflammation resolution, Efferocytosis

Abbreviations: Ang-(1-7): Angiotensin-(1-7); MasR: Mas receptor; SPMs: Specialized Proresolving Mediators; PMN: Polymorphonuclear Neutrophils; M1: Classically Activated Macrophages; M2: Alternatively Activated Macrophages; Mres: Proresolving Macrophages; TGF-β: Transforming Growth Factor-β (TGF-β); IL: Interleukin; CCR: C-C Motif Chemokine Receptor; CCL: C-C Motif Chemokine Ligand; MEK/ERK: Mitogen-activated Protein Kinases; COPD: Chronic Obstructive Pulmonary Disease; LPS: Lipopolysaccharide

Angiotensin-(1-7) Production and Action

Angiotensin-(1-7) [Ang-(1-7)] is a bioactive component of the renin-angiotensin system (RAS) that counteracts the actions of angiotensin II (Ang II) by exerting vasodilatory, anti-inflammatory [1], antifibrotic [2,3], and tissue-protective effects [4]. Ang-(1-7) is generated from Ang I through neprilysin (NEP), prolylendopeptidase (PEP), or thimet oligopeptidase (TOP) activity; from Ang II via angiotensin-converting enzyme 2 (ACE2), prolylcarboxypeptidase (PRCP), or prolylendopeptidase (PEP); and from Ang-(1-9) through ACE or NEP, as shown in **Figure 1** [5–8].

The autocrine and paracrine effects of Ang-(1-7) are mainly mediated by the G protein–coupled receptor Mas (MasR) [9], which is expressed in various tissues, including the heart, brain, kidney, and lungs [10], as well as in immune cells such as macrophages [11–13]. By interacting with MasR, Ang-(1-7) has been shown to decrease infiltration of neutrophils, eosinophils, and lymphocytes, thereby reducing tissue damage caused by excessive inflammation in preclinical models of arthritis [14], asthma [15,16], pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), and acute lung injury [17,18], ischemic stroke [19], ultimately preventing several features of inflammation [11,20]. Interestingly, a single dose of Ang-(1-7) promotes lung inflammation resolution and provides lasting protection against secondary challenges with allergens or endotoxin by enhancing IL-10, regulatory T cells, and macrophage efferocytosis [18].

Ang-(1-7) exhibits anti-inflammatory effects primarily by suppressing the release of key pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 [11,21], and by limiting the migration and activation of inflammatory cells [14,22]. It also promotes the generation of nitric oxide (NO) [23] and anti-inflammatory prostanoids [24], contributing to the maintenance of tissue homeostasis. Beyond anti-inflammatory actions, Ang-(1-7) displays pro-resolving properties. It enhances efferocytosis [25] and phagocytic clearance of apoptotic neutrophils, favors macrophage reprogramming toward a regulatory phenotype [13], and helps terminate inflammation. Furthermore, Ang-(1-7) reduces fibroblast activation and pathological extracellular matrix accumulation, thereby preventing fibrosis [26,27]. Lipoxin A_4, a specialized pro-resolving mediator (SPM), has been shown to upregulate elements of the Ang-(1-7) axis—including ACE2, Ang-(1-7), and the Mas receptor—particularly in models of lung injury [28].

The Role of Macrophages in Inflammation and Resolution

Inflammation occurs in vascularized tissues after injury or infection and is characterized by edema and arrival of leukocytes to the damage site or bacterial entry point. This vital host defense mechanism helps eliminate pathogens effectively and supports tissue repair, ultimately restoring organ and tissue function [29,30]. Concomitantly, affected tissue shows decreased synthesis and enhanced catabolism of pro-inflammatory mediators, while generation and release of anti-inflammatory and proresolving mediators rise, providing the stage for the resolution of inflammation [31–33,34].

Resolution of inflammation is an active, tightly regulated process through which the organism actively ends the inflammatory response, restores homeostatic conditions, and begins repairing affected tissues [33,35]. Key steps for proper resolution of inflammation involve activation of several mediators and cellular processes that collectively drive the swift and complete restoration of tissue homeostasis, such as elimination of inciting stimulus, cessation of PMN influx, catabolism of proinflammatory mediators, PMN apoptosis, efferocytosis, non-phlogistic macrophage recruitment, macrophage phenotype reprogramming (from M1 to M2, and from M2 to Mres), and production of anti-inflammatory and pro-resolving mediators. For comprehensive reviews, see [1,33,36,37].

Seminal research by Elie Metchnikoff established the important role of macrophages in coordinating the host immune response [38,39]. Macrophages are essential for clearing pathogen and cellular debris from inflammatory sites and also aid resolve inflammation promoting tissue repair and regeneration [40]. Indeed, the role of macrophage in cleaning debris generated by cell death during inflammatory injury, which can promote immune cell activation amplifying the inflammatory response, is critical for maintenance of tissue integrity and avoidance of tissue self-harm [41,42].

The recruitment of macrophages is a hallmark of the resolution phase of acute inflammation with their numbers increasing in tissue in parallel with the drop of neutrophils [13,43,44], underscoring the key role of macrophage in clearing dead cells. In the resolution phase of acute inflammation a specific subset of macrophages emerges, playing a crucial role in restoring homeostasis by initiating the removal of apoptotic leukocytes through efferocytosis [45–47]. Notably, efferocytosis induces a functional rewiring of macrophage toward anti-inflammatory and pro-resolving profiles [48,49].

Although the classification of macrophage phenotypes has modified and grown in complexity significantly in recent years, traditionally, macrophages are classified into M1 (classical activation, involved in the beginning of inflammation) and M2 (alternative activation, anti-inflammatory) [50]. A so-called Mres or pro-resolving group of macrophages (endowed with tissue remodeling properties) has been identified at sites of inflammation during the resolution phase [43,48,49]. Whereas M2 IL-10-producing macrophages are known to be highly efferocytic and help resolve inflammation [51], Mres macrophages are described as satiated and poor efferocytic [48,49]. More recently, a new group of macrophages—named rejuvenated hyper-efferocytic Ly6C$^+$ macrophages—has been described and shown to be induced by IFN-β and to display enhanced efferocytic capacity via high CD36 receptor expression [52]. Overall, the arrival of macrophages with pro-resolving profiles promoting clearance of apoptotic death cells and debris, releasing anti-inflammatory/pro-resolving mediators, and promoting tissue repair/regeneration is crucial for termination of the inflammatory response and restoration of homeostasis.

Effects of Angiotensin- (1-7) on Macrophages

Groundbreaking research over the past few decades by various laboratories worldwide has revealed the anti-inflammatory and pro-resolving effects of Ang-(1-7) [1–3,11,13,14,16,20,21,25,53–57]. These biological actions of Ang-(1-7) are mediated through its interaction with the MasR [9], a receptor found in leukocytes, including macrophage [12,13] (see **Figure 1**).

Several studies have demonstrated that the Ang-(1-7)/MasR axis inhibits the ability of macrophages to produce pro-inflammatory cytokines [11,12,21,22]. Additionally, Ang-(1-7) increases the efferocytic ability of macrophages to clean up apoptotic neutrophils [13,25,54,56] and eosinophils [16] within inflammatory sites. In this commentary, we analyze the study by Zaidan *et al.* [13]. Using self-resolving models of acute inflammation induced by lipopolysaccharide (LPS) and *Escherichia coli*, the research group led by Sousa and Teixeira [13] employed both pharmacological tools and MasR knockout mice (MasR$^-$/$^-$) to show that Ang-(1-7) signaling promoted nonphlogistic migration of macrophage and their further polarization toward regulatory phenotypes (M2 and Mres). Ang-(1-7) enhanced efferocytosis of apoptotic neutrophils and phagocytosis of *E. coli* and facilitated the resolution of inflammation, actions that occurred via MasR. The authors also examined the underlying mechanisms, demonstrating that Ang-(1-7) stimulated cell migration though a CCL2/CCR2 sensitive pathway. In addition, these macrophages expressed Arginase-1 and YM1 (classical M2 markers) and released IL-10 and TGF-β, as represented in **Figure 2**.

Ang-(1-7) itself promoted chemotaxis of murine and human macrophages, but had no direct effect on the chemotaxis of neutrophils. In contrast, Ang-(1-7) inhibited chemotaxis of neutrophils toward fMLP and also decreased chemotaxis of macrophages toward LPS. The latter findings are in agreement with others showing that Ang-(1-7) could deactivate several pro-inflammatory functions of macrophages [11,22,58,59]. A recent study showed that Ang-(1-7) modulated the Warburg effect via the citrate pathway in LPS-stimulated macrophages and reduced inflammation and organ damage in septic mice [60].

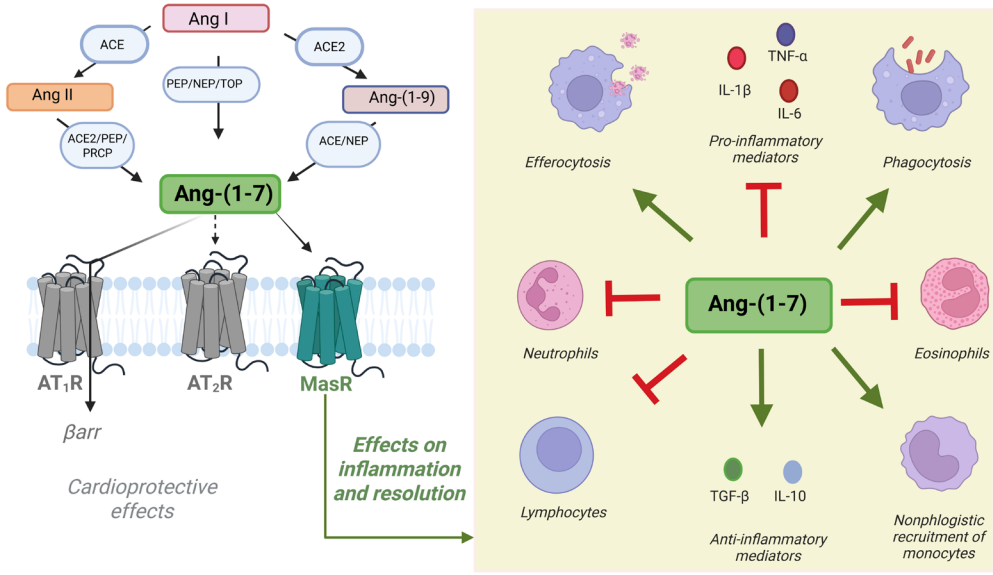

Figure 1. Biosynthesis of Ang-(1-7) and its effects on inflammation and resolution. Ang-(1-7) can be produced from Ang I, Ang II, or Ang-(1-9) through enzymatic cleavage by angiotensin-converting enzyme (ACE), ACE2, neprilysin (NEP), prolylendopeptidase (PEP), prolylcarboxypeptidase (PRCP), and thimet oligopeptidase (TOP). Once formed, Ang-(1-7) binds primarily to the Mas receptor (MasR), and to a lesser extent to AT_2R, exerting protective effects on inflammation and its resolution. Ang-(1-7) can also act as an endogenous β-arrestin-biased agonist at the AT_1R, causing cardioprotective effects without engaging its canonical G protein signaling pathway. Through MasR signaling, Ang-(1-7) enhances macrophage efferocytosis and phagocytosis, promotes production of anti-inflammatory mediators (TGF-β, IL-10), and facilitates non-phlogistic recruitment of monocytes. Simultaneously, it suppresses neutrophil activation, eosinophil responses, lymphocyte-driven inflammation, and reduces secretion of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6). Collectively, these actions establish Ang-(1-7) as a key regulator of immune balance and tissue homeostasis. Created in BioRender.

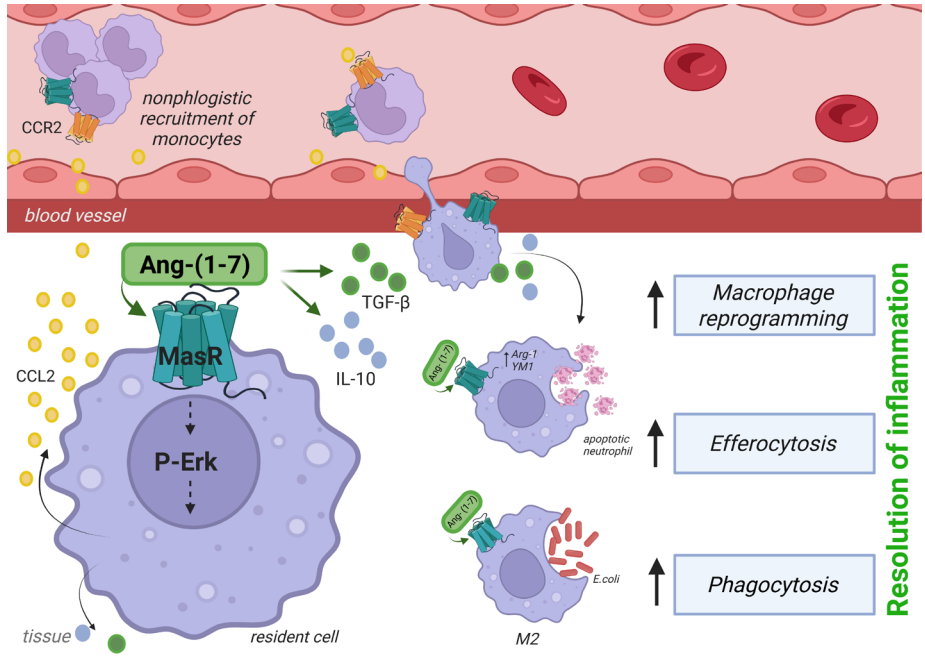

Figure 2. Ang-(1-7) promotes resolution of inflammation through Mas receptor (MasR) signaling in macrophages. Binding of Ang-(1-7) to MasR activates ERK1/2 phosphorylation and induces CCL2 production, leading to nonphlogistic recruitment of monocytes via CCR2. MasR signaling enhances the release of anti-inflammatory cytokines (TGF-β, IL-10) and stimulates macrophage effector functions, including efferocytosis of apoptotic neutrophils and phagocytosis of pathogens, thereby driving inflammation resolution and tissue repair. Created in BioRender.

In vivo injection of Ang-(1-7) in the plural cavity of mice promoted selective migration of monocytes/macrophages in a MasR- and the CCR2-dependent manner. Importantly, Ang-(1-7) activated the MEK/ERK1/2 pathway, leading to CCL2 production and further recruitment of mononuclear cells via CCR2 (**Figure 2**). Of Note, the chemokine CCL2 has been shown to promote M2 polarization [44,61–63] and macrophage-mediated clearance of apoptotic cells [64], actions needed for effective resolution of inflammation. Although CCR2 and MasR were co-expressed and needed for Ang-(1-7)-induced macrophage migration, the study did not establish whether Ang-(1-7) directly or indirectly interacted with CCR2 to drive chemotaxis, highlighting the need for further research to clarify these mechanisms.

In addition to showing that Ang-(1-7) could alter macrophage function to induce resolution of inflammation in response to LPS, the authors also showed that Ang-(1-7)- exposed macrophages could significantly increase *E. coli* engulfment and clearance. The latter effects could explain the decreased ability of MasR deficient mice to deal with infection. A recent study has shown that myeloid-specific MasR deficiency impairs efferocytosis and hampers inflammation resolution [47]. The loss of MasR reduced MERTK expression—a receptor essential for apoptotic cell clearance—thereby limiting macrophage-mediated removal of apoptotic neutrophils. Together with the findings of Zaidan *et al*. [13], these results underscore MasR signaling as a central regulator of efferocytosis and inflammation resolution. Of interest, follow up studies in our lab have extended these observations and shown Ang-(1-7)/MasR can promote phagocytosis and clearance of other bacteria, including *Pseudomonas aeruginosa* [56] and *Streptococcus pneumonia* [65].

Conclusion and Perspectives

In summary, the study by Zaidan *et al.* [13] addresses a key gap in our understanding of the Ang-(1-7)/MasR axis in macrophage-driven processes vital for resolving inflammation. These processes include the recruitment of macrophage endowed with a regulatory phenotype promoting clearance of apoptotic neutrophils and bacteria. The study also indicates that Ang-(1-7) improves macrophage antimicrobial functions while preventing excessive inflammation—an important feature with clear clinical implications for infection management—suggesting that combined treatment of Ang-(1-7) with antibiotics would improve bacterial resistance and resilience during infectious diseases. Indeed, adjunctive treatment with Ang-(1-7) and antibiotics during pneumonia induced by *Pseudomonas aeruginosa* [56] or *Streptococcus pneumonia* [65] improves the phagocytic ability of macrophages resulting in enhanced bacterial clearance and mice survival. In addition to altering the pathogenesis of bacterial infections, our group has also demonstrated that treatment with Ang-(1-7) lessened inflammation and lung injury caused by influenza and SARS-CoV-2 [54,57,66]. Additional insights into the therapeutic potential of Ang-(1-7) in infectious diseases can be found in Tavares *et al.* [1] and Costa *et al*, [34].

Finally, although we have learned a great deal about the crucial role of MasR and beneficial functions of Ang-(1-7) in the context of inflammatory and infectious diseases, there is much to learn about the detailed signaling mechanisms triggered by MasR signaling. This knowledge will be crucial to generate better molecules to be used in humans.

Conflict of Interests

The author declares no conflict of interest.

Acknowledgments

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