REGULATION OF INNATE IMMUNE CELLS BY POLYAMINES: A REVIEW

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Abstract
Polyamines, including spermine, spermidine, and putrescine, are small aliphatic cations essential for cellular growth, differentiation, and survival. Emerging evidence highlights their crucial role in regulating innate immune cells, where they modulate both protective and suppressive functions. In neutrophils, polyamines influence the formation and structural integrity of extracellular traps (NETs). In macrophages, they regulate polarization between pro-inflammatory M1 and anti-inflammatory M2 phenotypes, affecting immune responses in infection and tumor contexts. Mast cells, eosinophils, and basophils rely on polyamines for mediator release, granule maintenance, adhesion, and survival. In natural killer (NK) cells, polyamines can suppress cytotoxic activity by reducing receptor expression and effector molecule production, while also supporting maturation and proliferation through IL-2 modulation. In dendritic cells, polyamines promote a tolerogenic phenotype via IL-10 production and generate reactive oxygen species that inhibit maturation and antigen presentation. In epithelial cells, polyamines sustain TLR2 expression and barrier integrity, supporting mucosal immune homeostasis. Importantly, polyamines act as a double-edged sword, either enhancing or suppressing immune responses depending on cell type, microenvironment, and concentration. Dysregulated polyamine metabolism contributes to impaired innate immunity, chronic inflammation, and tumor immune evasion. Understanding these multifaceted roles offers potential therapeutic strategies for modulating innate immune function in disease.

Keywords: *Polyamines, innate immune response , Innate immune cells, regulation*

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Introduction

Polyamines are small aliphatic polycations present in virtually all living cells and are essential for many biological processes required for cellular growth, survival, and homeostasis (Pegg & McCann, 1982). Their discovery dates back to the seventeenth century when spermine crystals were first observed in cooled human semen by Antonie van Leeuwenhoek. In mammals, the major biologically active polyamines—putrescine, spermidine, and spermine—are produced through sequential enzymatic reactions beginning with putrescine and are tightly regulated through coordinated processes of biosynthesis, transport, and degradation to maintain intracellular balance (Pegg, 2013; Abdulhussein & Wallace, 2014; Miller-Fleming et al., 2015). Alterations in polyamine metabolism have been reported in several pathological conditions, including tissue injury and cancer, highlighting their importance in cellular physiology and disease development (Nakanishi & Cleveland, 2021; Mandal et al., 2015). Due to their positive charge at physiological pH, polyamines interact with negatively charged macromolecules such as DNA, RNA, and proteins, enabling them to regulate key cellular processes including proliferation, differentiation, autophagy, and immune cell activation (Pegg, 2009). Previous studies have extensively explored the role of polyamines in adaptive immune responses, particularly in T and B lymphocytes, where they influence differentiation and functional activity (Bowlin et al., 1987; Pasquali et al., 1988; Carriche et al., 2021; Puleston et al., 2021). However, despite growing recognition of their immunomodulatory properties, the specific roles and regulatory mechanisms of polyamines within innate immune cells remain insufficiently understood. Therefore, this review aims to summarize and analyze current evidence regarding the involvement of polyamines in innate immune cell function, highlighting existing knowledge while addressing the remaining gaps in this field.

Role of Polyamines in Innate immune cells

1. Neutrophil

Neutrophils represent the first line of defense against invading microbes and parasites, employing multiple antimicrobial mechanisms including phagocytosis, production of reactive oxygen species (ROS), and release of antimicrobial molecules. In addition to these classical functions, the discovery of neutrophil extracellular traps (NETs) has added a critical dimension to neutrophil-mediated immunity (Brinkmann et al., 2004). Upon exposure to inflammatory stimuli, neutrophils undergo a specialized form of cell death known as NETosis, during which they release decondensed chromatin into the extracellular space, forming web-like structures capable of trapping and neutralizing pathogens. This process is initiated through activation of surface receptors such as Toll-like receptors (TLRs), Fc receptors, and complement receptors, leading to intracellular calcium influx, activation of protein kinase C, and subsequent ROS generation (Stoiber et al., 2015). These signaling events promote nuclear and granular membrane disintegration, allowing the mixing of their contents and facilitating chromatin decondensation. A key step in this process involves histone citrullination mediated by peptidylarginine deiminase 4 (PAD4), ultimately resulting in the release of NET structures (Csomós et al., 2016).

Emerging evidence suggests that polyamines may influence neutrophil function, particularly in the regulation of NET formation. Due to their polycationic nature, polyamines can interact with negatively charged components of chromatin and proteins, potentially affecting the structural integrity of NETs. Notably, competitive inhibition of protein cross-linking by monoamines has been shown to disrupt the organized architecture of NET proteins, leading to impaired NET formation and a reduced ability to trap bacteria (Csomós et al., 2016).

2. Macrophage

Macrophages are professional phagocytic cells that play a central role in maintaining tissue homeostasis through the clearance of cellular debris, apoptotic cells, and invading pathogens (Murray&Wynn, 2011). Functionally, macrophages exhibit remarkable plasticity and are broadly classified into two major phenotypes: classically activated M1 macrophages, which are pro-inflammatory and involved in host defense, and alternatively activated M2 macrophages, which are associated with anti-inflammatory responses and tissue repair (Najafi et al., 2019). Within the tumor immune microenvironment (TIME), macrophage polarization is dynamically regulated by cytokines produced by tumor and stromal cells. In the early stages of tumor development, M1 macrophages promote inflammation and exert anti-tumor effects. However, as tumors progress, these cells are often reprogrammed into M2-like tumor-associated macrophages (TAMs) under the influence of cytokines such as IL-10, IL-4, and IL-13 (Shapouri-Moghaddam et al., 2018). These M2 macrophages contribute to immunosuppression, angiogenesis, and fibrosis, thereby facilitating tumor progression (Murray & Wynn, 2011).Polyamines have emerged as important regulators of macrophage polarization and function. Accumulating evidence indicates that polyamines, particularly putrescine and spermidine, modulate macrophage responses by suppressing pro-inflammatory activity and promoting an anti-inflammatory phenotype. For example, putrescine has been shown to inhibit M1 macrophage activation by downregulating the expression of key pro-inflammatory cytokines such as IL-8 and TNF-α in lipopolysaccharide (LPS)-stimulated models, which may contribute to tumor immune evasion (Liu et al., 2019; Latour et al., 2020). Similarly, spermidine reduces the expression of co-stimulatory molecules, including CD80 and CD86, and decreases the production of pro-inflammatory cytokines, thereby attenuating M1-associated functions (Yang et al., 2016). In addition, spermidine promotes macrophage polarization toward the M2 phenotype through mechanisms involving mitochondrial reactive oxygen species generation, activation of AMP-activated protein kinase (AMPK), upregulation of hypoxia-inducible factor-1α (HIF-1α), and induction of autophagy (Yang et al., 2016). Collectively, these findings highlight the critical role of polyamines in shaping macrophage polarization and suggest their potential contribution to immune regulation within inflammatory and tumor-associated environments.

3.Mast cell

Mast cells are key components of both innate and adaptive immunity, contributing to host defense as well as a wide range of physiological and pathological processes, including allergy, asthma, atherosclerosis, autoimmune diseases, and cancer (Galli et al., 2005; Yu et al., 2006). Their functional versatility is largely attributed to their ability to release a diverse array of inflammatory mediators. Many of these mediators are preformed and stored within cytoplasmic secretory granules and can be rapidly released upon stimulation, particularly following crosslinking of immunoglobulin E (IgE) bound to the high-affinity FcεRI receptor. These granules contain biogenic amines such as histamine and serotonin, proteases including tryptases and chymases, as well as cytokines (Galli et al., 2005). Structurally, mast cell granules are rich in proteoglycans, predominantly serglycin, which consists of negatively charged glycosaminoglycan chains that facilitate the storage and stabilization of these mediators (Stevens & Austen, 1989; Åbrink et al., 2004).

Polyamines have been increasingly recognized as important modulators of mast cell function. Early studies demonstrated that spermine and spermidine can directly influence mast cell degranulation. At higher concentrations, these polyamines induce rapid histamine release, whereas at lower concentrations they enhance IgE-mediated degranulation responses (Kurosawa et al., 1990; 1991). This effect has been attributed, at least in part, to the activation of phosphatidylinositol kinase signaling pathways involved in granule exocytosis. Furthermore, polyamines are closely associated with the structural organization of mast cell granules. They are localized within secretory granules and interact with serglycin to maintain granule integrity and proper storage of mediators such as histamine and serotonin. Disruption of polyamine synthesis using inhibitors like DFMO leads to altered granule ultrastructure and impaired storage capacity, resembling the effects observed with serglycin depletion (García-Faroldi et al., 2010). In addition, the identification of a vesicular polyamine transporter (VPAT) has provided further insight into the regulated storage and release of polyamines in mast cells (Takeuchi et al., 2017).

4.Eosinophils and Basophile

Eosinophils are important granulocytes involved in allergic inflammation and asthma pathology, where their survival and activation significantly contribute to disease progression. Emerging evidence indicates that polyamines, particularly spermine, play a crucial role in regulating eosinophil lifespan and function. Spermine has been shown to prolong eosinophil survival by inhibiting apoptosis in both healthy and asthmatic subjects, with a median effective concentration of approximately 15 μmol/L (Ilmarinen et al., 2015). Mechanistically, this effect is associated with the inhibition of mitochondrial permeability transition (mPT) and suppression of both initiator (caspases 8 and 9) and effector (caspases 3/7) apoptotic pathways. Among polyamines, spermine exhibits the strongest activity, followed by spermidine, while

putrescine appears to have minimal or no effect on eosinophil survival. In addition to enhancing cell viability, spermine upregulates the expression of adhesion molecules such as CD11b, which are associated with increased functional responsiveness. Although spermine alone does not directly induce a strong oxidative response, it enhances the oxidative burst triggered by stimuli such as the bacterial chemotactic peptide N-formyl-methionyl-leucine-phenylalanine (FMLP), thereby amplifying eosinophil effector functions (Walker et al., 1993; Jain, 2018).

In basophilic cells and related mast cell lineages, polyamines are also implicated in the regulation of cellular function, proliferation, and mediator synthesis. The metabolism of polyamines is closely linked with histamine production, as both pathways are regulated by key enzymes, including ornithine decarboxylase (ODC) for polyamines and histidine decarboxylase (HDC) for histamine synthesis. Studies using non-transformed mouse mast cell lines have demonstrated a coordinated interplay between these pathways. Specifically, treatment with phorbol ester and dexamethasone results in increased histidine decarboxylase expression and elevated intracellular histamine levels, accompanied by a reduction in ornithine decarboxylase expression, decreased polyamine content, and suppressed cell proliferation (Fajardo et al., 2001).

5.Natural Killer (NK) Cells

Polyamines play a complex and context-dependent role in regulating natural killer (NK) cell functions, often described as a double-edged sword due to their dual immunosuppressive and immunostimulatory effects. Several studies have demonstrated that elevated polyamine levels can suppress NK cell activity by reducing their cytolytic capacity, thereby facilitating tumor immune evasion (Janakiram et al., 2016). In contrast, depletion of polyamines has been shown to enhance NK cell function, suggesting that endogenous polyamine levels critically influence NK cell-mediated immunity (Chamaillard et al., 1997). Mechanistically, polyamines can downregulate the expression of key activating receptors such as NK1.1, as well as decrease the production of cytotoxic molecules including perforin and interferon-gamma (IFN-γ), ultimately impairing the ability of NK cells to recognize and eliminate tumor cells. Notably, these inhibitory effects can be reversed by targeting polyamine metabolism using agents such as difluoromethylornithine (DFMO) and rosuvastatin (Janakiram et al., 2016).In addition to modulating receptor expression and effector molecule production, polyamines also influence NK cell adhesion and cytotoxic interactions. The adhesion molecule lymphocyte function-associated antigen-1 (LFA-1) plays a crucial role in NK cell activation by binding to intercellular adhesion molecule-1 (ICAM-1) on target cells, facilitating cytoskeletal polarization and effective delivery of cytotoxic granules (Urlaub et al., 2017). However, spermine has been shown to impair NK cell function by reducing LFA-1 expression and weakening LFA-1/ICAM-1 interactions, thereby diminishing cytotoxic efficiency (Soda et al., 2005).Conversely, polyamines may also exert supportive effects on NK cell biology under certain conditions. They have been implicated in promoting NK cell differentiation, maturation, and survival. For instance, polyamine biosynthesis has been associated with increased production of interleukin-2 (IL-2), a cytokine known to enhance NK cell proliferation and cytotoxic activity (Levin et al., 2012; Flescher et al., 1989)

6.Dendritic cells

Dendritic cells (DCs) are bone marrow–derived antigen-presenting cells that reside in virtually all tissues and serve as key sentinels of the immune system, bridging innate and adaptive immunity (Banchereau & Steinman, 1998). Their function is tightly regulated by environmental cues, including cytokines, pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs), which are sensed through a variety of surface and intracellular receptors (Schlitzer et al., 2015). DCs play a crucial role in anti-tumor immunity by capturing tumor-associated antigens and cross-presenting them to T cells in tumor-draining lymph nodes, leading to the activation of tumor-specific cytotoxic T lymphocytes (CTLs) (Fuertes et al., 2011). However, within the tumor immune microenvironment (TIME), multiple immunosuppressive signals can impair DC maturation and antigen-presenting capacity. For instance, anti-inflammatory cytokines such as IL-10 inhibit DC maturation and promote antigen-specific T cell anergy, while certain tumor-associated antigens, including carcinoembryonic antigen (CEA) and mucin-1 (MUC1), may be retained within early endosomes, thereby limiting their proper processing and presentation (Hiltbold et al., 2000).Polyamines have emerged as significant modulators of DC function, particularly in the context of tumor-associated immune suppression. Arginase-1 (ARG1), a key enzyme in polyamine biosynthesis, is highly expressed in DCs and contributes to immune evasion by depleting local arginine levels, which in turn inhibits T cell proliferation through downregulation of the CD3-ζ chain of the T cell receptor (Gabrilovich & Nagaraj, 2009; Mondanelli et al., 2017). Furthermore, polyamines such as spermine and spermidine can skew DCs toward a tolerogenic phenotype by enhancing IL-10 production, thereby promoting the induction of anergic $CD8^+$ T cells (Haskó et al., 2000). In addition to these direct effects, polyamine catabolism generates reactive oxygen species (ROS), which can further impair DC function. Elevated ROS levels in the tumor microenvironment can inhibit antigen cross-presentation and interfere with DC maturation, partly through the induction of endoplasmic reticulum stress (Casero & Pegg, 2009; Paardekooper et al., 2019; Chougnet et al., 2015).

7. Epithelial cells

Epithelial cells are a fundamental component of the innate immune system, serving not only as a physical barrier but also as active participants in immune surveillance and response. In the intestinal mucosa, epithelial cells protect

underlying tissues from a wide range of pathogens, allergens, and harmful substances. Beyond forming a mechanical barrier, intestinal epithelial cells (IECs) actively sense the luminal environment through pattern recognition receptors (PRRs), produce antimicrobial peptides, and release cytokines and chemokines to orchestrate immune cell recruitment (Sitaraman et al., 2001). Among PRRs, Toll-like receptors (TLRs) are critical for recognizing conserved microbial structures and some endogenous molecules, thereby initiating innate immune responses (Abreu et al., 2005; Anderson, 2000).

Polyamines have emerged as key regulators of epithelial innate immunity, particularly through their influence on TLR2 expression. Experimental studies have shown that polyamines are essential for maintaining basal TLR2 levels and enabling TLR2 activation in response to stimuli such as low-dose lipopolysaccharide (LPS). Importantly, this regulatory effect is specific to TLR2, as polyamine levels do not affect TLR4 expression. Polyamine depletion not only reduces basal TLR2 expression but also impairs its inducible activation, which in turn can compromise epithelial barrier function (Chen et al., 2007). These findings highlight the role of polyamines as biological regulators that help maintain mucosal homeostasis and the integrity of the epithelial barrier under physiological conditions.

Although the precise molecular mechanisms remain unclear, evidence suggests that polyamines moduleTLR2 expression at the transcriptional level, as supported by studies in IECs and other epithelial models (Liu et al., 2005; Liu et al., 2006; Xiao et al., 2007). This transcriptional regulation likely underpins the ability of polyamines to support both immune sensing and barrier integrity in intestinal epithelia.Most research on polyamines has been conducted in isolated cells or ex vivo models, which may not fully capture the complexity of immune responses in vivo. Their effects are highly context-dependent, varying with cell type, concentration, and microenvironment, making outcomes difficult to predict. Mechanistic understanding remains limited, particularly regarding transcriptional and epigenetic regulation, and clinical validation in humans is still scarce. In addition, in tumor and chronic inflammation settings, polyamines interact with multiple pathways, complicating the identification of their direct effects. These limitations highlight the need for more in vivo and clinical studies to clarify their roles and therapeutic potential.

Conclusions

Polyamines play a central role in regulating innate immunity by controlling phagocytosis, mediator release, cytotoxicity, and cell survival. Their effects are context-dependent, capable of both enhancing and suppressing immune responses depending on the cell type and microenvironment. They modulate macrophage polarization, NK cell function, dendritic cell tolerance, and epithelial barrier integrity. Dysregulated polyamine metabolism contributes to impaired immunity, chronic inflammation, and tumor progression, highlighting their potential as therapeutic targets for modulating innate immune responses.

References

1. Abdulhussein, A. A.,&Wallace, H. M. (2014). Polyamines and membrane transporters. *Amino acids*, *46*(3), 655-660.
2. Abreu, M. T., Fukata, M., & Arditi, M. (2005). TLR signaling in the gut in health and disease. *The Journal of Immunology*, *174*(8), 4453-4460.
3. Åbrink, M., Grujic, M., & Pejler, G. (2004). Serglycin is essential for maturation of mast cell secretory granule. Journal of biological chemistry, 279(39), 40897-40905.
4. Anderson, K. V. (2000). Toll signaling pathways in the innate immune response. *Current opinion in immunology*, *12*(1), 13-19.
5. Banchereau, J.,&Steinman, R. M. (1998). Dendritic cells and the control of immunity. *Nature*, *392*(6673), 245-252.
6. Bowlin, T. L., McKown, B. J., & Sunkara, P. S. (1987). Increased ornithine decarboxylase activity and polyamine biosynthesis are required for optimal cytolytic T lymphocyte induction. *Cellular immunology*, *105*(1), 110-117.
7. Brinkmann, V., Reichard, U., Goosmann, C., Fauler, B., Uhlemann, Y., Weiss, D. S., ... & Zychlinsky, A. (2004). Neutrophil extracellular traps kill bacteria. *science*, *303*(5663), 1532-1535.
8. Carriche, G. M., Almeida, L., Stüve, P., Velasquez, L., Dhillon-LaBrooy, A., Roy, U., ... & Sparwasser, T. (2021). Regulating T-cell differentiation through the polyamine spermidine. *Journal of Allergy and Clinical Immunology*, *147*(1), 335-348.
9. Casero Jr, R. A., & Pegg, A. E. (2009). Polyamine catabolism and disease. *Biochemical Journal*, *421*(3), 323-338.
10. Chamaillard, L., Catros-Quemener, V., Delcros, J. G., Bansard, J. Y., Havouis, R., Desury, D., ... & Moulinoux, J. P. (1997). Polyamine deprivation prevents the development of tumour-induced immune suppression. *British journal of cancer*, *76*(3), 365-370.
11. Chen, J., Rao, J. N., Zou, T., Liu, L., Marasa, B. S., Xiao, L., ...&Wang, J. Y. (2007). Polyamines are required for expression of Toll-like receptor 2 modulating intestinal epithelial barrier integrity. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, *293*(3), G568-G576.
12. Chougnet, C. A., Thacker, R. I., Shehata, H. M., Hennies, C. M., Lehn, M. A., Lages, C. S.,&Janssen, E. M. (2015). Loss of phagocytic and antigen cross-presenting capacity in aging dendritic cells is associated with mitochondrial dysfunction. *The Journal of Immunology*, *195*(6), 2624-2632.

13. Csomós, K., Kristóf, E., Jakob, B., Csomós, I., Kovács, G., Rotem, O., Hodrea, J., Bagoly, Z., Muszbek, L., Balajthy, Z., Csősz, É., & Fésüs, L. (2016). Protein cross-linking by chlorinated polyamines and transglutamylation stabilizes neutrophil extracellular traps. *Cell death&disease*, *7*(8), e2332. https://doi.org/10.1038/cddis.2016.200.
14. DD, M. (1997). Mast cells. *Physiol Rev*, *77*, 1033-1079.
15. Fajardo, I., Urdiales, J. L., Medina, M. A., & Sanchez-Jimenez, F. (2001). Effects of phorbol ester and dexamethasone treatment on histidine decarboxylase and ornithine decarboxylase in basophilic cells. *Biochemical pharmacology*, *61*(9), 1101-1106.
16. Flescher, E. L. I. E. Z. E. R., Bowlin, T. L., & Talal, N. O. R. M. A. N. (1989). Polyamine oxidation down-regulates IL-2 production by human peripheral blood mononuclear cells. *The Journal of Immunology*, *142*(3), 907-912.
17. Fuertes, M. B., Kacha, A. K., Kline, J., Woo, S. R., Kranz, D. M., Murphy, K. M., & Gajewski, T. F. (2011). Host type I IFN signals are required for antitumor CD8+ T cell responses through CD8α+ dendritic cells. *Journal of Experimental Medicine*, *208*(10), 2005-2016.
18. Gabrilovich, D. I.,&Nagaraj, S. (2009). Myeloid-derived suppressor cells as regulators of the immune system. *Nature reviews immunology*, *9*(3), 162-174.
19. Galli, S. J., Kalesnikoff, J., Grimbaldeston, M. A., Piliponsky, A. M., Williams, C. M., & Tsai, M. (2005). Mast cells as "tunable" effector and immunoregulatory cells: recent advances. *Annu. Rev. Immunol.*, *23*(1), 749-786.
20. Galli, S. J., Nakae, S.,&Tsai, M. (2005). Mast cells in the development of adaptive immune responses. *Nature immunology*, *6*(2), 135-142.
21. García-Faroldi, G., Rodríguez, C. E., Urdiales, J. L., Pérez-Pomares, J. M., Dávila, J. C., Pejler, G., ...&Fajardo, I. (2010). Polyamines are present in mast cell secretory granules and are important for granule homeostasis. *PLoS One*, *5*(11), e15071.
22. Haskó, G., Kuhel, D. G., Marton, A., Nemeth, Z. H., Deitch, E. A., & Szabó, C. (2000). Spermine differentially regulates the production of interleukin-12 p40 and interleukin-10 and suppresses the release of the T helper 1 cytokine interferon-γ. *Shock*, *14*(2), 144-149.
23. Hiltbold, E. M., Vlad, A. M., Ciborowski, P., Watkins, S. C.,&Finn, O. J. (2000). The mechanism of unresponsiveness to circulating tumor antigen MUC1 is a block in intracellular sorting and processing by dendritic cells. *The Journal of Immunology*, *165*(7), 3730-3741.
24. Ilmarinen, P., Moilanen, E., Erjefält, J. S., & Kankaanranta, H. (2015). The polyamine spermine promotes survival and activation of human eosinophils. *Journal of Allergy and Clinical Immunology*, *136*(2), 482-484.
25. Jain, V. (2018). Role of polyamines in asthma pathophysiology. *Medical Sciences*, *6*(1), 4.
26. Janakiram, N. B., Mohammed, A., Bryant, T., Zhang, Y., Brewer, M., Duff, A., ... & Rao, C. V. (2016). Potentiating NK cell activity by combination of Rosuvastatin and Difluoromethylornithine for effective chemopreventive efficacy against Colon Cancer. *Scientific reports*, *6*(1), 37046.
27. Kurosawa, M., Uno, D.,&Kobayashi, S. (1991). Naturally occurring aliphatic polyamines-induced histamine release from rat peritoneal mast cells. *Allergy*, *46*(5), 349-354.
28. Kurosawa, M., Uno, D., Hanawa, K.,&Kobayashi, S. (1990). Polyamines stimulate the phosphorylation of phosphatidylinositol in rat mast cell granules. *Allergy*, *45*(4), 262-267.
29. Latour, Y. L., Gobert, A. P.,&Wilson, K. T. (2020). The role of polyamines in the regulation of macrophage polarization and function. *Amino Acids*, *52*(2), 151-160.
30. Leeuwenhoek, A. V. (1978). Observationes D. Anthonii Lewenhoeck, de natis è semine genitali animalculis. *Philosophical Transactions of the Royal Society of London*, *12*(142), 1040-1046.
31. Levin, A. M., Bates, D. L., Ring, A. M., Krieg, C., Lin, J. T., Su, L., ...&Garcia, K. C. (2012). Exploiting a natural conformational switch to engineer an interleukin-2 'superkine'. *Nature*, *484*(7395), 529-533.
32. Liu, B., Jiang, X., Cai, L., Zhao, X., Dai, Z., Wu, G.,&Li, X. (2019). Putrescine mitigates intestinal atrophy through suppressing inflammatory response in weanling piglets. *Journal of animal science and biotechnology*, *10*(1), 69.
33. Liu, L., Guo, X., Rao, J. N., Zou, T., Marasa, B. S., Chen, J., ...&Wang, J. Y. (2006). Polyamine-modulated c-Myc expression in normal intestinal epithelial cells regulates p21Cip1 transcription through a proximal promoter region. *Biochemical Journal*, *398*(2), 257-267.
34. Liu, L., Li, L., Rao, J. N., Zou, T., Zhang, H. M., Boneva, D., ...&Wang, J. Y. (2005). Polyamine-modulated expression of c-myc plays a critical role in stimulation of normal intestinal epithelial cell proliferation. *American Journal of Physiology-Cell Physiology*, *288*(1), C89-C99.
35. Mandal, S., Mandal, A., & Park, M. H. (2015). Depletion of the polyamines spermidine and spermine by overexpression of spermidine/spermine N 1-acetyltransferase 1 (SAT1) leads to mitochondria-mediated apoptosis in mammalian cells. *Biochemical Journal*, *468*(3), 435-447.
36. Miller-Fleming, L., Olin-Sandoval, V., Campbell, K., & Ralser, M. (2015). Remaining mysteries of molecular biology: the role of polyamines in the cell. *Journal of molecular biology*, *427*(21), 3389-3406.
37. Mondanelli, G., Ugel, S., Grohmann, U.,&Bronte, V. (2017). The immune regulation in cancer by the amino acid metabolizing enzymes ARG and IDO. *Current opinion in pharmacology*, *35*, 30-39.

38. Murray, P. J.,&Wynn, T. A. (2011). Protective and pathogenic functions of macrophage subsets. *Nature reviews immunology*, *11*(11), 723-737.
39. Murray, P. J.,&Wynn, T. A. (2011). Protective and pathogenic functions of macrophage subsets. *Nature reviews immunology*, *11*(11), 723-737.
40. Najafi, M., Hashemi Goradel, N., Farhood, B., Salehi, E., Nashtaei, M. S., Khanlarkhani, N., ... & Mortezaee, K. (2019). Macrophage polarity in cancer: a review. *Journal of cellular biochemistry*, *120*(3), 2756-2765.
41. Nakanishi, S.,&Cleveland, J. L. (2021). Polyamine homeostasis in development and disease. *Medical Sciences*, *9*(2), 28.
42. Paardekooper, L. M., Vos, W., & Van Den Bogaart, G. (2019). Oxygen in the tumor microenvironment: effects on dendritic cell function. *Oncotarget*, *10*(8), 883.
43. Pasquali, J. L., Mamont, P. S., Weryha, A., Knapp, A. M., Blervaque, A., & Siat, M. (1988). Immunosuppressive effects of (2R, 5R)-6-heptyne-2, 5-diamine an inhibitor of polyamine synthesis: I. effects on mitogen-induced immunoglobulin production in human cultured lymphocytes. *Clinical and experimental immunology*, *72*(1), 141.
44. Pegg, A. E. (2009). Mammalian polyamine metabolism and function. *IUBMB life*, *61*(9), 880-894.
45. Pegg, A. E. (2013). Toxicity of polyamines and their metabolic products. *Chemical research in toxicology*, *26*(12), 1782-1800.
46. Pegg, A. E.,&McCann, P. P. (1982). Polyamine metabolism and function. *American Journal of Physiology-Cell Physiology*, *243*(5), C212-C221.
47. Proietti, E., Rossini, S., Grohmann, U., & Mondanelli, G. (2020). Polyamines and kynurenines at the intersection of immune modulation. *Trends in immunology*, *41*(11), 1037-1050.
48. Puleston, D. J., Baixauli, F., Sanin, D. E., Edwards-Hicks, J., Villa, M., Kabat, A. M., ...&Pearce, E. L. (2021). Polyamine metabolism is a central determinant of helper T cell lineage fidelity. *Cell*, *184*(16), 4186-4202.
49. Schlitzer, A., McGovern, N., & Ginhoux, F. (2015, May). Dendritic cells and monocyte-derived cells: Two complementary and integrated functional systems. In *Seminars in cell&developmental biology* (Vol. 41, pp. 9-22). Academic Press.
50. Shapouri-Moghaddam, A., Mohammadian, S., Vazini, H., Taghadosi, M., Esmaeili, S. A., Mardani, F., ... & Sahebkar, A. (2018). Macrophage plasticity, polarization, and function in health and disease. *Journal of cellular physiology*, *233*(9), 6425-6440.
51. Sitaraman, S. V., Merlin, D., Wang, L., Wong, M., Gewirtz, A. T., Si-Tahar, M., & Madara, J. L. (2001). Neutrophil-epithelial crosstalk at the intestinal lumenal surface mediated by reciprocal secretion of adenosine and IL-6. *The Journal of clinical investigation*, *107*(7), 861-869.
52. Soda, K., Kano, Y., Nakamura, T., Kasono, K., Kawakami, M., & Konishi, F. (2005). Spermine, a natural polyamine, suppresses LFA-1 expression on human lymphocyte. *The Journal of Immunology*, *175*(1), 237-245.
53. Stevens, R. L.,&Austen, K. F. (1989). Recent advances in the cellular and molecular biology of mast cells. *Immunology today*, *10*(11), 381-386.
54. Stoiber, W., Obermayer, A., Steinbacher, P., & Krautgartner, W. D. (2015). The role of reactive oxygen species (ROS) in the formation of extracellular traps (ETs) in humans. *Biomolecules*, *5*(2), 702-723.
55. Takeuchi, T., Harada, Y., Moriyama, S., Furuta, K., Tanaka, S., Miyaji, T., ... & Hiasa, M. (2017). Vesicular polyamine transporter mediates vesicular storage and release of polyamine from mast cells. *Journal of Biological Chemistry*, *292*(9), 3909-3918.
56. Urlaub, D., Höfer, K., Müller, M. L., & Watzl, C. (2017). LFA-1 activation in NK cells and their subsets: influence of receptors, maturation, and cytokine stimulation. *The Journal of Immunology*, *198*(5), 1944-1951.
57. Vliagoftis, H., Boucher, W. S., Mak, L. L., & Theoharides, T. C. (1992). Inhibition of mast cell secretion by oxidation products of natural polyamines. *Biochemical pharmacology*, *43*(10), 2237-2245.
58. Walker, C., Rihs, S., Braun, R. K., Betz, S., & Bruijnzeel, P. L. (1993). Increased expression of CD11b and functional changes in eosinophils after migration across endothelial cell monolayers. *The Journal of Immunology*, *150*(9), 4061-4071.
59. Xiao, L., Rao, J. N., Zou, T., Liu, L., Marasa, B. S., Chen, J., ... & Wang, J. Y. (2007). Induced JunD in intestinal epithelial cells represses CDK4 transcription through its proximal promoter region following polyamine depletion. *Biochemical Journal*, *403*(3), 573-581.
60. Yang, Q., Zheng, C., Cao, J., Cao, G., Shou, P., Lin, L., ...&Shi, Y. (2016). Spermidine alleviates experimental autoimmune encephalomyelitis through inducing inhibitory macrophages. *Cell Death&Differentiation*, *23*(11), 1850-1861.
61. Yu, M., Tsai, M., Tam, S. Y., Jones, C., Zehnder, J.,&Galli, S. J. (2006). Mast cells can promote the development of multiple features of chronic asthma in mice. *The Journal of clinical investigation*, *116*(6), 1633-1641.