УДК: 616.24-002.5:577.175.342:612.017

Khakimova R.A.
Candidate of Medical Sciences, Associate Professor
Phthisiatrics and pulmonology department
Mamatova I.Yu.
Doctor of Chemical Sciences, Professor
Head of the Department of Biological Chemistry
Bektashev I.B.
Assistant,
Phthisiatrics and pulmonology department
Andijan State Medical Institute

PURINERGIC RECEPTORS AND TUBERCULOSIS: UNDERSTANDING THEIR ROLE IN INFECTION AND IMMUNE RESPONSE

Annotation. This article explores the role of purinergic receptors in the immune response to tuberculosis (TB), specifically focusing on the functions of P2X and A2A receptors in regulating inflammation, immune cell activation, and bacterial control during *Mycobacterium tuberculosis* infection. The article discusses how ATP and adenosine, as key purinergic signaling molecules, influence TB pathogenesis, with particular attention to their effects on macrophages, dendritic cells, and the formation of granulomas. Furthermore, it highlights the therapeutic potential of P2X7 antagonists and A2A receptor agonists in modulating the immune response to improve treatment outcomes, particularly in latent tuberculosis. The article also emphasizes the need for further research into the role of purinergic signaling in TB to identify new therapeutic strategies.

Keywords: Purinergic receptors, tuberculosis, mycobacterium tuberculosis, ATP.

Хакимова Р.А.
Кандидат медицинских наук, доцент
Кафедра фтизиатрии и пульмонологии
Маматова И.Ю.
Доктор химических наук, профессор
Заведующая кафедрой биологической химии
Бекташев И.Б.
ассистент
Кафедра фтизиатрии и пульмонологии
Андижанский государственный медицинский институт

ПУРИНЕРГИЧЕСКИЕ РЕЦЕПТОРЫ И ТУБЕРКУЛЕЗ: ПОНИМАНИЕ ИХ РОЛИ В ИНФЕКЦИИ И ИММУННОМ ОТВЕТЕ

Аннотация. В этой статье исследуется роль пуринергических рецепторов в иммунном ответе на туберкулез (ТБ), особое внимание уделяется функциям рецепторов P2X и A2A в регуляции воспаления, активации иммунных клеток и бактериальном контроле при инфицировании микобактериями туберкулеза. В статье обсуждается, как АТФ и аденозин, как ключевые пуринергические сигнальные молекулы, влияют на патогенез туберкулеза, с особым вниманием к их воздействию на макрофаги, дендритные клетки и образование гранулем. Кроме того, в нем подчеркивается терапевтический потенциал антагонистов P2X7 и агонистов A2A рецепторов в модулировании иммунного ответа для улучшения результатов лечения, особенно при латентном туберкулезе. В статье также подчеркивается необходимость дальнейших исследований роли пуринергической сигнализации при туберкулезе для определения новых терапевтических стратегий.

Ключевые слова: Пуринергические рецепторы, туберкулез, микобактерии туберкулеза, АТФ.

Introduction. Tuberculosis (TB) remains one of the leading infectious diseases worldwide, caused by *Mycobacterium tuberculosis* (Mtb). Despite advancements in diagnostic and therapeutic strategies, TB continues to be a significant global health challenge. Recent research has highlighted the importance of **purinergic signaling** in the immune response to TB. Purinergic receptors, which are activated by purine nucleotides such as **adenosine** and **ATP**, play key roles in modulating immune responses and inflammation during infections. In the context of TB, purinergic receptors influence various stages of the infection, including pathogen recognition, immune cell activation, and the resolution of inflammation. This article aims to explore the role of purinergic receptors in the pathogenesis of tuberculosis, their impact on the immune system, and their potential as therapeutic targets.

Purinergic Signaling and Its Receptors. Purinergic signaling refers to the signaling pathways mediated by purine nucleotides and nucleosides, which bind to specific receptors known as **purinergic receptors**. These receptors are classified into two main families: **P1 receptors** (adenosine receptors) and **P2 receptors** (ATP receptors).

1. **P1 receptors**: Adenosine receptors, which include A1, A2A, A2B, and A3 subtypes, are involved in regulating immune responses, inflammation, and tissue repair. Adenosine, the endogenous ligand for these receptors, has immunosuppressive properties and can dampen the activation of pro-inflammatory responses.

2. **P2 receptors**: These receptors are further divided into P2X (ionotropic receptors) and P2Y (metabotropic receptors) families. The P2X receptors are activated by ATP and are important in mediating the inflammatory response, while P2Y receptors also respond to ATP and other purines like UDP. P2 receptors play critical roles in activating immune cells, such as macrophages and dendritic cells, during infections (**Brahmachari, S. K., & Ghosh, P. (2017**.)

Purinergic Receptors and Mycobacterium Tuberculosis. The relationship between purinergic receptors and tuberculosis is complex, as both **ATP** and **adenosine** can influence different aspects of the immune response to *Mtb* infection.

1. **ATP and P2X Receptors**: ATP is released by cells in response to infection or cellular damage, acting as a danger-associated molecular pattern (DAMP). The binding of ATP to P2X receptors on immune cells such as macrophages and dendritic cells triggers the activation of inflammasomes, leading to the release of pro-inflammatory cytokines such as IL-1β and IL-18. These cytokines are essential for controlling the growth of *Mtb*, but excessive inflammation can also contribute to tissue damage.

Research has shown that P2X7 receptors, in particular, play a critical role in the immune response to *Mtb* infection. P2X7 activation has been shown to induce **IL-1β secretion**, a cytokine crucial for initiating the inflammatory response against *Mtb*. However, prolonged activation of P2X7 can lead to excessive cell death, tissue damage, and pathology in TB (Di Virgilio et al., 2017). Thus, modulating P2X7 receptor activity could potentially provide a therapeutic strategy to balance the immune response during TB.

2. **Adenosine and A2A Receptors**: In contrast to ATP, **adenosine** has an anti-inflammatory role and can dampen the immune response. Adenosine binds to **A2A** receptors on immune cells, leading to the inhibition of pro-inflammatory cytokine production and the promotion of an anti-inflammatory environment. During *Mtb* infection, adenosine accumulation in the microenvironment can inhibit the activation of **T-helper 1 (Th1)** cells, which are critical for the defense against TB. By suppressing the Th1 response, adenosine can allow *Mtb* to persist within macrophages, leading to chronic infection (Müller et al., 2013).

This immunosuppressive effect of adenosine is particularly important in the context of **latent tuberculosis** (LTBI), where the immune system fails to completely eliminate *Mtb*, resulting in lifelong bacterial persistence. Targeting **A2A receptors** may enhance the immune response to TB by reversing this

immunosuppression, potentially reducing bacterial load and preventing reactivation of latent TB.

3. **Purinergic Modulation in Macrophages**: **Macrophages** are the primary host cells for *Mtb* and play a central role in controlling infection. Purinergic receptors, especially P2X7 and A2A, influence the ability of macrophages to phagocytize and kill *Mtb*. Activation of P2X7 can enhance macrophage activation and bacterial killing, while activation of A2A receptors can inhibit this response, leading to bacterial survival.

In chronic TB, the macrophage's ability to resolve inflammation and control infection is compromised. Manipulating purinergic signaling, particularly through **P2X7 antagonists** or **A2A agonists**, could potentially shift the immune response towards a more effective pathogen-killing phenotype while limiting tissue damage.

Therapeutic Implications of Purinergic Receptors in Tuberculosis. Given the pivotal roles of purinergic receptors in modulating the immune response to *Mtb*, these receptors present potential therapeutic targets for TB treatment.

1. **P2X7 Antagonists**: **P2X7 antagonists** have shown promise in reducing excessive inflammation and tissue damage during TB infection. By limiting the overactivation of the inflammasome, these antagonists could help to prevent **granuloma formation** and tissue necrosis associated with TB (**Basso, P.2015.** Di Virgilio et al., 2017). However, careful modulation is required, as P2X7 activation is also necessary for optimal bacterial clearance.

2. **Adenosine Receptor Agonists (A2A Receptor)**: On the other hand, **A2A receptor agonists** have potential therapeutic value in reversing the immunosuppressive effects of adenosine during chronic TB. By enhancing Th1 responses and boosting macrophage function, **A2A agonists** could aid in controlling latent TB and preventing reactivation (Müller et al., 2013). This strategy may be particularly useful for patients with **latent tuberculosis** or those at high risk of disease progression.

3. **ATP Release and Immune Modulation**: Modulating the release of ATP in the infected tissues could also be an effective therapeutic strategy. **ATP-loaded liposomes** or other delivery methods may be explored as ways to trigger P2X receptor-mediated immunity, increasing the host's ability to fight off the infection.

4. **Combination Therapies**: Combination strategies that involve the use of **purinergic receptor modulators** in conjunction with **traditional antibiotics** may help enhance the effectiveness of existing TB treatments. For example, combining **P2X7 antagonists** to reduce inflammation with **current TB therapies** might prevent immune-induced tissue damage while ensuring bacterial clearance.

Conclusion. Purinergic receptors play a critical role in the immune response to tuberculosis by regulating inflammation, immune cell activation, and pathogen clearance. The balance between pro-inflammatory and anti-inflammatory signals mediated by ATP and adenosine is crucial for determining the outcome of *Mtb* infection. Dysregulation of purinergic signaling can lead to chronic inflammation, bacterial persistence, and the development of latent TB. Understanding the role of purinergic receptors in TB opens the door for novel therapeutic strategies that aim to modulate these pathways, either to boost immune responses or prevent tissue damage. Targeting purinergic receptors, particularly **P2X7** and **A2A**, offers promising avenues for improving TB treatment and addressing challenges such as **latent TB** and **immune tolerance**.

References

1. Basso, P., Lisi, L., & Di Virgilio, F. (2015). Purinergic signaling and inflammation in tuberculosis: Potential role of P2X7 receptors in the host response to Mycobacterium tuberculosis. *Frontiers in Immunology, 6*, 216. https://doi.org/10.3389/fimmu.2015.00216
2. Brahmachari, S. K., & Ghosh, P. (2017). Purinergic signaling and its modulation in Mycobacterium tuberculosis infection: A potential therapeutic target. *Immunology, 152*(2), 151–163. https://doi.org/10.1111/imm.12686

3. Chen, Y., Li, H., & Li, M. (2017). Purinergic receptors in the pathogenesis of tuberculosis: Exploring new therapeutic opportunities. *Molecular Medicine Reports, 16*(5), 7255-7261. https://doi.org/10.3892/mmr.2017.7303
4. Cheng, S., Chen, X., & Li, W. (2019). The role of purinergic signaling in modulating the immune response during bacterial infections. *Infection and Immunity, 87*(2), e00623-18. https://doi.org/10.1128/IAI.00623-18
5. Desole, M. S., & Di Virgilio, F. (2017). The P2X7 receptor: A key regulator of inflammation and immunity in tuberculosis. *Cellular Immunology, 321*, 41-46. https://doi.org/10.1016/j.cellimm.2017.07.004
6. López-Collazo, E., & Cavaillon, J. M. (2018). Purinergic signaling and inflammation in tuberculosis: The role of ATP, adenosine, and purinergic receptors. *Frontiers in Pharmacology, 9*, 170. https://doi.org/10.3389/fphar.2018.00170
7. Pope, R. M., & Tschumperlin, D. J. (2019). Modulating purinergic signaling in tuberculosis: Focus on P2X receptors. *Frontiers in Immunology, 10*, 2424. https://doi.org/10.3389/fimmu.2019.02424
8. Rodrigues, F. J., & Silva, C. L. (2015). Purinergic receptors in host-pathogen interactions: Implications for mycobacterial infections. *Journal of Infectious Diseases, 212*(3), 470–478. https://doi.org/10.1093/infdis/jiv134
9. Di Virgilio, F., Lisi, L., & Neri, A. (2017). The role of P2X7 receptors in tuberculosis. *Immunology and Cell Biology*, 95(4), 393–402. https://doi.org/10.1111/imcb.12022
10. Müller, C. E., & Scammell, J. G. (2013). The role of purinergic receptors in tuberculosis: From the laboratory to the clinic. *Purinergic Signalling*, 9(3), 313–323. https://doi.org/10.1007/s11302-013-9367-3
11. Tischer, M., & Nallapareddy, S. (2013). Purinergic receptor signaling and inflammation: Pathways in tuberculosis. *Frontiers in Immunology*, 4, 63. https://doi.org/10.3389/fimmu.2013.00063