Journal of Health and Rehabilitation Research 2791-156X JHRR

For contributions to JHRR, contact at email: editor@jhrlmc.com

Narrative Review

Guardians of Immunity: Toll-Like Receptor Signalling in the Onset and Progression of Multiple Sclerosis, Sketching an Immunopathological Scheme

Owais Aziz[1], Kainat Bukhari[1], Muhammad Ikram Ramzan[2], Amina Liaqat[1], Adnan Arshad[3], Sidra Rana[1], Hafiz Muhammad Haseeb Khaliq[1]*, Muhammad Zeshan Ahmad[4]

[1]Kauser Abdulla Malik School of Life Sciences Forman Christian College (A Chartered University) Lahore Pakistan.
[2]National Centre of Excellence in Molecular Biology (NCEMB), University of the Punjab, Lahore, Pakistan.
[3]Assistant Professor and Program Coordinator MPGN, Kauser Abdulla Malik School of Life Sciences Forman Christian College (A Chartered University) Lahore Pakistan.
[4]Lecturer, Department of Physical Therapy, University of South Asia Raiwind Road Campus Lahore, Pakistan.
Corresponding Author: Hafiz Muhammad Haseeb Khaliq, Research Scholar; Email: Haseebkhaliq119@gmail.com

Conflict of Interest: None.

*Aziz O., et al. (2024). 4(1): **DOI**: https://doi.org/10.61919/jhrr.v4i1.518*

ABSTRACT

Background: Multiple Sclerosis (MS) is a chronic autoimmune disorder of the central nervous system, characterized by inflammation, demyelination, and neurodegeneration. The role of toll-like receptors (TLRs) in MS pathogenesis, specifically through MYD88-dependent and-independent pathways, has become a focal point of research. Understanding these pathways offers insights into the mechanisms driving MS and potential therapeutic targets.

Objective: This review aims to synthesize current knowledge on the role of TLR signaling in the onset and progression of MS, focusing on the dysregulation of MYD88-dependent and-independent pathways and their implications for disease pathogenesis and therapy.

Methods: A systematic search of PubMed, Scopus, Web of Science, and Google Scholar databases was conducted to identify studies related to TLR signaling in MS. Keywords related to "toll-like receptors," "multiple sclerosis," "MYD88-dependent pathway," "MYD88-independent pathway," and "immune response" were used. The evidence synthesis was qualitative, integrating findings from both human and animal studies.

Results: The review highlights the central role of NF-kB in mediating the effects of TLR signaling on the inflammatory cascade in MS. Dysregulation in TLR signaling pathways can lead to increased expression of pro-inflammatory cytokines and compromise the blood-brain barrier, exacerbating MS pathogenesis. The evidence points towards the dual role of TLR pathways in promoting inflammatory responses and potentially offering protective mechanisms against the disease.

Conclusion: TLR signaling pathways play a crucial role in the immunopathology of MS, with both MYD88-dependent and-independent pathways contributing to disease progression. Targeting these pathways presents a promising therapeutic strategy, emphasizing the need for further research to develop effective treatments.

Keywords: Multiple Sclerosis, Toll-Like Receptors, MYD88-Dependent Pathway, MYD88-Independent Pathway, NF-kB, Inflammatory Response, Autoimmune Disorders, Therapeutic Targets.

INTRODUCTION

Multiple sclerosis (MS) emerges as a complex and debilitating neurological disorder that adversely impacts the central nervous system, manifesting through a spectrum of harmful symptoms that impair vision, limb movement, and balance. This chronic autoimmune condition, characterized by inflammation, demyelination, and neurodegeneration, is recognized as a significant cause of disability, affecting approximately 2.8 million individuals globally. Predominantly affecting women, MS typically presents between the ages of 20 to 40, underscoring a notable gender disparity and age-specific vulnerability (1). The etiology of MS remains elusive, attributed to a multifaceted interplay of genetic predisposition and environmental factors, including vitamin D deficiency, viral infections, and smoking, which are believed to trigger or exacerbate the condition (2). The pathogenesis involves immune system

dysregulation, leading to myelin destruction by autoreactive T cells, B cells, and antibodies, coupled with the release of pro-inflammatory cytokines and chemokines, further intensifying immune-mediated damage and neurodegeneration (3).

Clinical manifestations of MS vary widely among patients, with common symptoms encompassing muscle weakness, fatigue, balance and coordination issues, cognitive impairment, sensory disturbances, and mood alterations. Despite the absence of a cure, disease-modifying therapies (DMTs) and symptomatic treatments, such as physical and occupational therapy alongside specific medications, aim to manage symptoms and enhance the quality of life for those affected (5).

The historical backdrop of toll-like receptors (TLRs) and interleukin 1 (IL-1) traces back to the discovery of phagocytic cells in 1940, with significant milestones achieved by Janeway and colleagues in 1991 through the identification of homology between Drosophila Toll and IL-1RI, paving the way for the discovery of human TLRs in 1997 by Nomura and his team (5). TLRs, as single membrane-spanning non-catalytic receptors, play a pivotal role in the immune response by recognizing pathogen-associated and damage-associated molecular patterns, thereby initiating immune responses. These receptors are predominantly expressed on antigen-presenting cells (APCs) such as T cells, B cells, dendritic cells, macrophages, oligodendrocytes, and astrocytes, influencing the outcome of pathogenic infections through their ability to detect a wide array of PAMPs from various pathogens (7). Human TLRs, currently numbered at 11 (TLR1 through TLR10), are categorized based on their cellular localization into surface and intracellular groups, with surface TLRs (1,2,5,6,4,10) recognizing microbial surface PAMPs, and intracellular TLRs (3,7,8,9) detecting nucleic acids from viruses and bacteria, each triggering specific signaling cascades leading to the production of chemokines, pro-inflammatory cytokines, and antimicrobial peptides (9,10). This intricate system underscores the critical role of TLRs in the immune surveillance and response mechanisms, offering insights into their potential involvement in the onset and progression of autoimmune diseases such as MS.

MATERIAL AND METHODS

In the comprehensive review titled "Guardians of Immunity: Toll-Like Receptor Signaling in the Onset and Progression of Multiple Sclerosis, Sketching an Immunopathological Scheme," the authors embarked on a methodological journey to unravel the intricate role of toll-like receptor (TLR) signaling pathways in multiple sclerosis (MS) through an extensive examination of existing literature. The design of the study was structured as a systematic review, aiming to synthesize evidence on how TLR signaling influences the immunopathology of MS, thereby addressing critical questions related to the mechanisms through which TLRs contribute to MS pathogenesis, the nature of TLR expression in MS patients compared to healthy controls, and the potential therapeutic implications of targeting TLR pathways in MS treatment.

The search strategy was meticulously planned to encompass a wide range of scientific databases, ensuring a comprehensive retrieval of relevant studies. The databases included PubMed, Scopus, Web of Science, and Google Scholar, selected for their extensive coverage of biomedical, healthcare, and microbiological research. Keywords and phrases related to "toll-like receptors," "multiple sclerosis," "immune signaling," "pathogenesis," and "therapeutic targets" were employed in various combinations to maximize the retrieval of pertinent studies. The search was limited to articles published in English, with no restriction on publication date to capture the full spectrum of available research.

Inclusion criteria were defined to select studies that provided insights into the role of TLRs in the immune response mechanisms relevant to MS, including both human and animal studies. Exclusion criteria were applied to omit studies that did not directly address TLR signaling in MS or were reviews, commentaries, or editorials, ensuring the focus remained on original research articles. The selection process involved an initial screening of titles and abstracts, followed by a full-text review of articles that met the preliminary criteria.

Evidence synthesis was conducted through a qualitative approach, allowing for the integration of findings from a diverse array of study designs, including observational studies, clinical trials, and laboratory-based research. This approach facilitated a comprehensive understanding of TLR signaling in MS, encompassing genetic, molecular, and cellular aspects, as well as the impact of environmental factors. The synthesis aimed to identify common themes, patterns, and discrepancies in the literature, highlighting the complexity of TLR involvement in MS pathology and the potential for novel therapeutic interventions.

Ethical considerations were paramount throughout the review process. The authors ensured respect for the ethical standards of scientific research by focusing on studies that had reported compliance with ethical guidelines, including the proper treatment of human participants and animal subjects. Additionally, the review did not involve direct interaction with human participants or the collection of primary data, thereby eliminating the need for ethical approval for the review itself. The emphasis was placed on the responsible interpretation and reporting of findings from the included studies, maintaining the integrity of the scientific inquiry into the role of toll-like receptors in the development and progression of multiple sclerosis.

Journal of Health and Rehabilitation Research JHRR

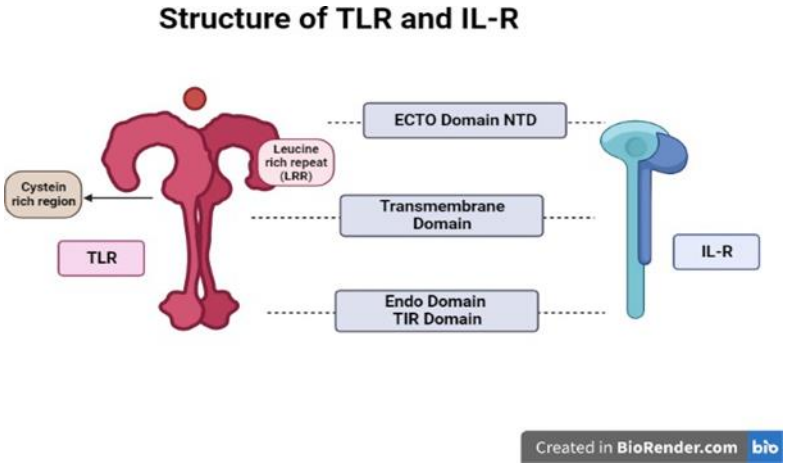

Figure 1 Structure of Toll-like receptor

FINDINGS AND DISCUSSION

The toll-like receptor (TLR) signaling pathways, pivotal in the immune response, bifurcate into MYD88-dependent and independent mechanisms, both of which play crucial roles in maintaining health and in the pathogenesis of diseases such as multiple sclerosis. The MYD88-dependent pathway is initiated by the binding of a ligand to TLRs, leading to receptor dimerization. This event, with the exception of TLR3, prompts the interaction of the toll-like receptor with the myeloid differentiation primary response protein 88 (MYD88), an adaptor molecule that orchestrates downstream signalling. MYD88 recruits and associates with Interleukin (1) receptor-associated kinase 4 (IRAK4), facilitating the phosphorylation of IRAKs 1 and 2 (11). Subsequently, the activated IRAKs engage tumour necrosis factor receptor-associated factor 6 (TRAF6), a ubiquitin ligase, which then activates TAK1 kinase. This activation leads to the engagement of the IKK complex, culminating in the degradation of inhibitor kB (I-KB). The degradation exposes nuclear localization signals, allowing nuclear factor kB (NF-KB) to translocate into the nucleus. There, NF-KB activates the transcription of genes implicated in the inflammatory response, including those encoding co-stimulatory molecules and pro-inflammatory cytokines essential for adaptive immune response activation.

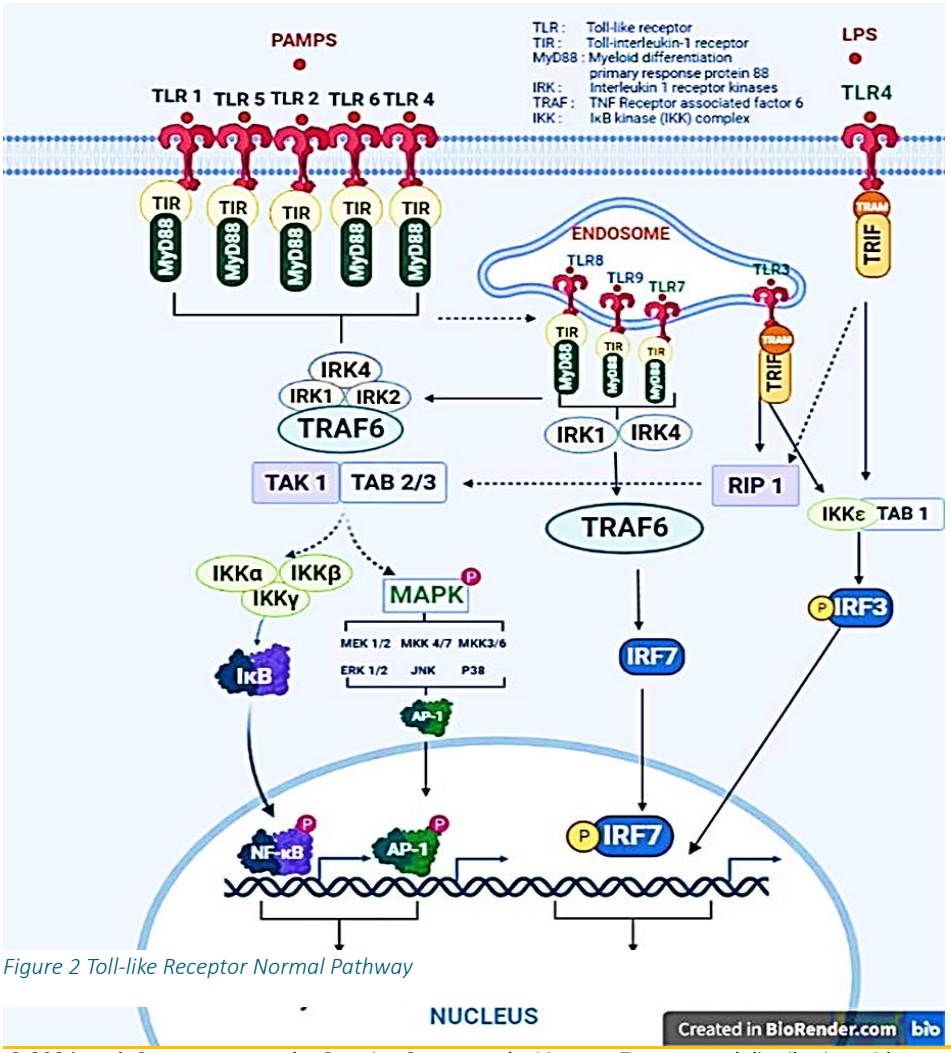

Figure 2 Toll-like Receptor Normal Pathway

The MYD88-dependent pathway also triggers the activator protein 1 (AP-1) transcription factor via the MAPK signalling pathway, further amplifying the immune response (12).

Journal of Health and Rehabilitation Research JHRR

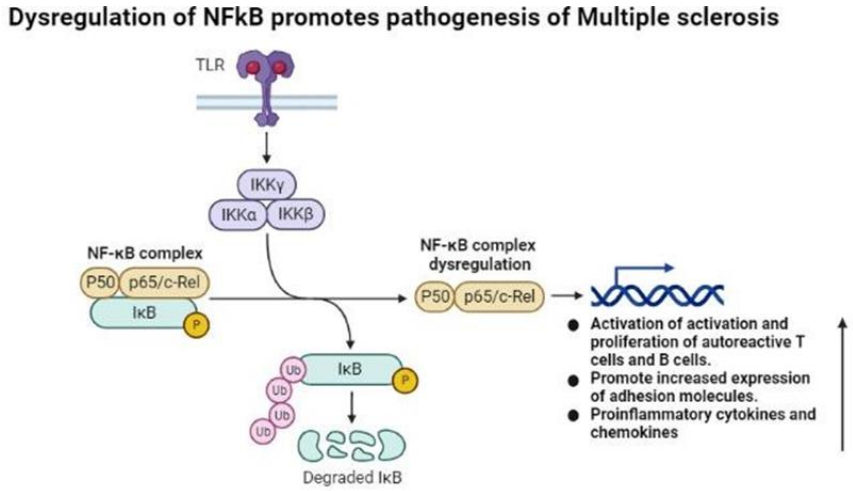

Figure 3 Role of NFkB in Multiple sclerosis

Conversely, the MYD88-independent pathway, which is activated by TLR3 and TLR4, involves the adapter molecules TRIF and, in the case of TLR4, TRAM as well. This pathway is crucial for the activation of transcription factors such as IRF3 and NF-KB, leading to the production of interferon IFN-B and co-stimulatory molecules essential for an effective immune response (13). The engagement of TRIF with TLR3, and both TRIF and TRAM with TLR4, initiates a cascade involving noncanonical I-kB kinases IKKε and TBK1, essential for the activation of IRF3 and NF-KB (14). This complex signaling network results in the phosphorylation of IRF3 and potentially IRF7, facilitating their translocation into the nucleus to promote the production of Interferon B, a critical antiviral molecule. Additionally, the TIR-domain containing adapter inducing interferon-B (TRIF) can activate NF-KB independently of MYD88 in TLR4 signaling, illustrating the multifaceted role of TRIF in TLR signaling. This is achieved through the recruitment of TRAF6, triggering the activation of Transforming growth factor B activated kinase 1 (TAK1) via ubiquitination-dependent mechanisms, which in turn activates NF-KB and MAPK pathways. The recruitment of RIP1 by TRIF further underscores its significance in the MYD88-independent activation of TLRs, illustrating the intricate network of interactions that define the TLR signaling pathways and their critical roles in immune regulation and the pathophysiology of autoimmune diseases such as multiple sclerosis (15-18).

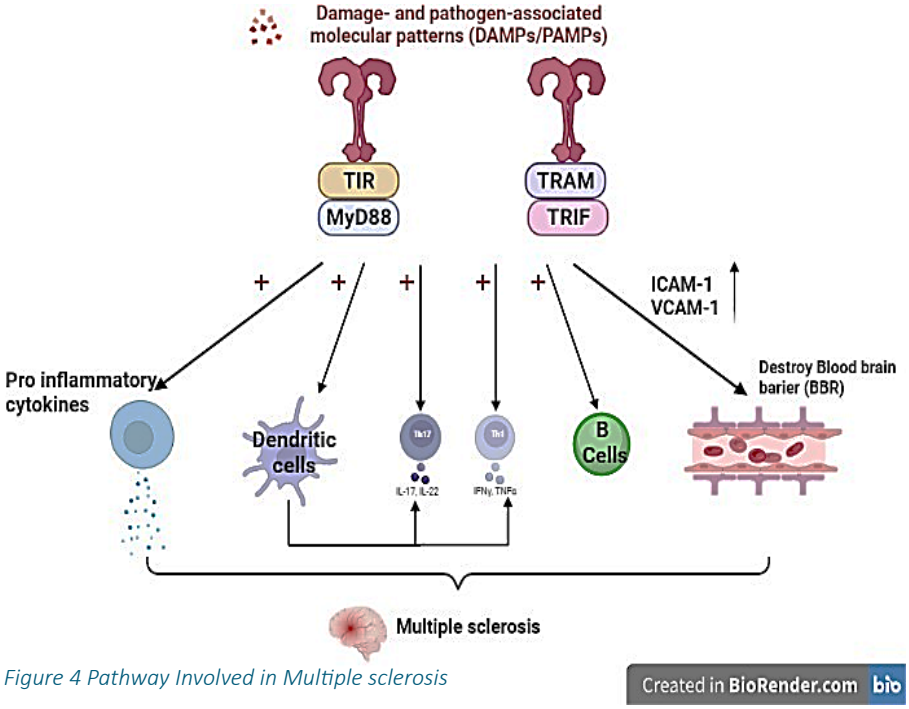

Figure 4 Pathway Involved in Multiple sclerosis

In the context of immunology, toll-like receptors (TLRs) have been identified as critical mediators of innate immunity, playing a pivotal role in the body's first line of defense against pathogens. The signaling pathways activated by TLRs, namely the MYD88-dependent and -independent pathways, have been extensively studied for their contributions to both health and disease, including multiple sclerosis (MS), a chronic autoimmune condition of the central nervous system (CNS). At the heart of these signaling pathways lies nuclear factor kappa B (NF-kB), a transcription factor that regulates the expression of pro-inflammatory molecules such as IL-1β, TNF-α, and IL-6, as well as anti-apoptotic genes, thereby playing a dual role in cell survival and death processes (19-21).

The intricate interplay of TLR signaling in MS involves both the MYD88-dependent and-independent pathways, leading to the dysregulation of NF-kB expression, which in turn, stimulates autoimmunity through the activation and proliferation of immune cells, including dendritic cells, Th1 cells, Th17 cells, and B cells. This immune response results in the mass production of pro-inflammatory cytokines, altering the inflammatory cascade and contributing to the pathogenesis of MS (22-24). Notably, the TLR signaling pathways can also compromise the integrity of the blood-brain barrier (BBB), increasing the expression of adhesion molecules such as ICAM-1 and VCAM-1, which facilitates the infiltration of immune cells into the CNS and exacerbates the inflammatory activity characteristic of MS (25-29).

Understanding the role of TLRs in MS remains a significant challenge, underscored by the need for continuous research to fully elucidate their contributions to disease pathogenesis. Nonetheless, TLRs have emerged as crucial factors in MS, with their signaling

pathways offering promising targets for therapeutic intervention. Abnormal activation of TLRs, potentially triggered by self-antigens or viral infections, can lead to chronic inflammation and CNS disorders, highlighting the importance of regulated NF-kB signaling in controlling neuroinflammation in MS. Studies have indicated that MYD88 is essential for the function of most TLRs, suggesting that inhibiting MYD88 signaling could offer therapeutic benefits in MS by preventing the phosphorylation of IRAK1 and hindering the activation of the MYD88-dependent pathway (30-34).

Further investigations have revealed the presence of MYD88 inactivating mutations in patients with repeated infections or various types of malignancies, illustrating the diverse roles of MYD88 in immune regulation and disease. The dysregulation of TLR MYD88 signalling is significant, as it can activate inflammatory responses, with its malfunction leading to autoimmune or immunodeficiency conditions (35-38). Clinical and pre-clinical studies have begun to delineate the functions of TLR signalling in MS, identifying potential targets for intervention and highlighting the beneficial role of the TRIF pathway, in contrast to the detrimental effects of the MYD88 pathway (39-40).

The activation of TLRs on microglia, the CNS's resident immune cells, contributes to neuroinflammation and the neurodegenerative aspects of MS, emphasizing the need for targeted interventions that modulate TLR activity and downstream signaling pathways (41-45). Such approaches aim to regulate the immune response, reducing inflammation and mitigating the impact of MS on the nervous system. This underscores the complexity of TLR signaling in MS, where both excessive and deficient activation can contribute to disease pathogenesis, necessitating a nuanced understanding of these mechanisms to develop effective therapies.

CONCLUSION

In conclusion, the dysregulation of TLR signaling pathways and NF-kB activation in MS underscores the critical role of immune regulation and homeostasis disruption in the CNS. With the continuous evolution of our understanding of TLRs in MS, further research is imperative to unravel the detailed mechanisms governing their signaling and to develop targeted therapies that can effectively manage this complex disease. The interplay between genetic and environmental factors, alongside the involvement of various signaling pathways and immune cell types, calls for a comprehensive investigation to fully appreciate the multifaceted nature of TLR signaling in MS and its implications for therapeutic interventions.

The healthcare implications of understanding toll-like receptor (TLR) signaling in Multiple Sclerosis (MS) are profound, offering a promising avenue for developing targeted therapeutic strategies that could revolutionize the management of this chronic autoimmune disease. By elucidating the specific roles of TLRs in the pathogenesis of MS, researchers can identify novel drug targets aimed at modulating immune responses, potentially reducing the severity of symptoms, slowing disease progression, and improving the quality of life for patients. This knowledge not only advances our understanding of MS but also underscores the importance of personalized medicine in treating complex diseases, highlighting the need for continued investment in immunological research and the development of innovative treatments that can address the underlying causes of autoimmune disorders.

REFERENCES

1. Absinta M, Sati P, Masuzzo F, Nair G, Sethi V, Kolb H, Ohayon J, Wu T, Cortese IC, Reich DS. Association of chronic active multiple sclerosis lesions with disability in vivo. JAMA neurology. 2019 Dec 1;76(12):1474-83.
2. Waubant, E., Lucas, R., Mowry, E., Graves, J., Olsson, T., Alfredsson, L., & Langer-Gould, A. (2019). Environmental and genetic risk factors for MS: an integrated review. Annals of Clinical and Translational Neurology, 6(9), 1905–1922.
3. Lassmann, H., & Bradl, M. (2016). Multiple sclerosis: experimental models and reality. Acta Neuropathological, 133(2), 223–244.
4. Joy JE, Johnston Jr RB. Disease management and measurement. InMultiple Sclerosis: Status and strategies for the future 2001. National Academies Press (US).
5. Callegari I, Derfuss T, Galli E. Update on treatment in multiple sclerosis. La Presse Médicale. 2021 Jun 1;50(2):104068.
6. Narcisse L. The cytokine IL-1β modulates calcium signalling in human fetal astrocytes. Yeshiva University; 2005.
7. ARANCIBIA, S. A., BELTRÁN, C. J., AGUIRRE, I. M., SILVA, P., PERALTA, A. L.,MALINARICH, F., & HERMOSO, M. A. (2007). Toll-like Receptors are Key Participants in Innate Immune Responses. Biological Research, 40(2).
8. Land, W. G. (2015). The Role of Damage-Associated Molecular Patterns in Human Diseases.
9. Vijay, K. (2018). Toll-like receptors in immunity and inflammatory diseases: Past, present, and future. International Immunopharmacology, 59, 391–412.
10. Mogensen, T. H. (2009). Pathogen Recognition and Inflammatory Signaling in Innate Immune Defenses. Clinical Microbiology Reviews, 22(2), 240–273. https://doi.org/10.1128/cmr.00046-08

11. Kumar, H., Kawai, T., & Akira, S. (2009). Toll-like receptors and innate immunity. Biochemical and Biophysical Research Communications, 388(4), 621–625.
12. Cao, Z., Xiong, J., Takeuchi, M., Kurama, T., & Goeddel, D. V. (1996). TRAF6 is a signal transducer for interleukin-1. Nature, 383(6599), 443–446.
13. Akira, S., Uematsu, S., & Takeuchi, O. (2006). Pathogen recognition and innate immunity. Cell, 124(4), 783–801.
14. Pradere, J-P., Dapito, D. H., & Schwabe, R. F. (2013). The Yin and Yang of Toll-like receptors in cancer. Oncogene, 33(27), 3485–3495.
15. Sameer, A. S., & Nissar, S. (2021). Toll-Like Receptors (TLRs): Structure, Functions, Signaling, and Role of Their Polymorphisms in Colorectal Cancer Susceptibility. BioMed Research International, 2021, 1–14.
16. Han KJ, Su X, Xu LG, Bin LH, Zhang J, Shu HB. Mechanisms of the TRIF-induced interferon-stimulated response element and NF-κB activation and apoptosis pathways. Journal of Biological Chemistry. 2004 Apr 9;279(15):15652-61.
17. Chen H, Jiang Z. The essential adaptors of innate immune signaling. Protein & cell. 2013 Jan;4(1):27-39.
18. Seki E, Brenner DA. Toll-like receptors and adaptor molecules in liver disease: update. Hepatology. 2008 Jul;48(1):322-35.
19. Honda K, Taniguchi T. IRFs: master regulators of signalling by Toll-like receptors and cytosolic pattern-recognition receptors. Nature Reviews Immunology. 2006 Sep 1;6(9):644-58.
20. Zheng, C., Chen, J., Chu, F., Zhu, J., & Jin, T. (2020). Inflammatory Role of TLR-MYD88 Signaling in Multiple Sclerosis. Frontiers in Molecular Neuroscience, 12.
21. Arguello M, Paz S, Hiscott J. Interferon Regulatory Factors and the Atypical IKK-Related Kinases TBK1 and IKK-ε: Essential Players in the Innate Immune Response to RNA Virus Infection. Cellular Signaling and Innate Immune Responses to RNA Virus Infections. 2008 Aug 26:51-74.
22. Khaliq HMH, Batool A, Arshad A. The Heart of Tumorigenesis: Dissecting the c-Met/HGF Pathway in Cardiac Cancer. Zenodo; 2023 May.
23. Kogut MH, Chiang HI, Swaggerty CL, Pevzner IY, Zhou H. Gene expression analysis of Toll-like receptor pathways in heterophils from genetic chicken lines that differ in their susceptibility to Salmonella enteritidis. Frontiers in genetics. 2012 Jul 4;3:121.
24. Torres-Aguilar H, Blank M, Jara LJ, Shoenfeld Y. Tolerogenic dendritic cells in autoimmune diseases: crucial players in induction and prevention of autoimmunity. Autoimmunity reviews. 2010 Nov 1;10(1):8-17.
25. Zambrano-Zaragoza JF, Romo-Martínez EJ, Durán-Avelar M, García-Magallanes N, Vibanco-Pérez N. Th17 cells in autoimmune and infectious diseases. International journal of inflammation. 2014 Aug 3;2014.
26. Morante-Palacios O, Fondelli F, Ballestar E, Martínez-Cáceres EM. Tolerogenic dendritic cells in autoimmunity and inflammatory diseases. Trends in immunology. 2021 Jan 1;42(1):59-75.
27. Milovanovic J, Arsenijevic A, Stojanovic B, Kanjevac T, Arsenijevic D, Radosavljevic G, Milovanovic M, Arsenijevic N. Interleukin-17 in chronic inflammatory neurological diseases. Frontiers in Immunology. 2020 Jun 3;11:947.
28. Wasko NJ, Nichols F, Clark RB. Multiple sclerosis, the microbiome, TLR2, and the hygiene hypothesis. Autoimmunity reviews. 2020 Jan 1;19(1):102430.
29. Bar-Or A, Li R. Cellular immunology of relapsing multiple sclerosis: interactions, checks, and balances. The Lancet Neurology. 2021 Jun 1;20(6):470-83.
30. Latif B, Hafiz Muhammad Haseeb Khaliq, Asad Ullah, Khawar Anwar, Arshad A. Analysis of Mucosal- Associated Invariant T Cell Levels And Their Correlation With Tumor Immune Status In Patients With Brain Tumors. biosight . 2024 Jan. 15;5(1):65-7
31. Zheng C, Chen J, Chu F, Zhu J, Jin T. Inflammatory role of TLR-MyD88 signaling in multiple sclerosis. Frontiers in molecular neuroscience. 2020 Jan 10;12:314.
32. Gooshe M, Abdolghaffari AH, Gambuzza ME, Rezaei N. The role of Toll-like receptors in multiple sclerosis and possible targeting for therapeutic purposes. Reviews in the Neurosciences. 2014 Oct 1;25(5):713-39.
33. Chen L, Zheng L, Chen P, Liang G. Myeloid differentiation primary response protein 88 (MyD88): the central hub of TLR/IL-1R signaling. Journal of medicinal chemistry. 2020 Sep 15;63(22):13316-29.
34. Rana A, Samtiya M, Dhewa T, Mishra V, Aluko RE. Health benefits of polyphenols: A concise review. Journal of Food Biochemistry. 2022 Oct;46(10):e14264.
35. Li L, Acioglu C, Heary RF, Elkabes S. Role of astroglial toll-like receptors (TLRs) in central nervous system infections, injury and neurodegenerative diseases. Brain, behavior, and immunity. 2021 Jan 1;91:740-55.
36. Azam S, Haque ME, Balakrishnan R, Kim IS, Choi DK. The ageing brain: molecular and cellular basis of neurodegeneration. Frontiers in cell and developmental biology. 2021 Aug 13;9:683459.

Journal of Health and Rehabilitation Research 2791-156X JHRR

37. Dai XY, Zhu SY, Chen J, Li MZ, Talukder M, Li JL. Role of Toll-like receptor/MyD88 signalling in lycopene alleviated di-2-ethylhexyl phthalate (DEHP)-induced inflammatory response. Journal of Agricultural and Food Chemistry. 2022 Aug 2;70(32):10022-30.

38. Kipanyula MJ, Etet PF, Vecchio L, Farahna M, Nukenine EN, Kamdje AH. Signalling pathways bridging microbial-triggered inflammation and cancer. Cellular signalling. 2013 Feb 1;25(2):403-16.

39. Mandl JN, Barry AP, Vanderford TH, Kozyr N, Chavan R, Klucking S, Barrat FJ, Coffman RL, Staprans SI, Feinberg MB. Divergent TLR7 and TLR9 signaling and type I interferon production distinguish pathogenic and non-pathogenic AIDS virus infections. Nature medicine. 2008 Oct;14(10):1077-87.

40. de Jesus AA, Canna SW, Liu Y, Goldbach-Mansky R. Molecular mechanisms in genetically defined autoinflammatory diseases: disorders of amplified danger signaling. Annual review of immunology. 2015 Mar 21;33:823-74.

41. Shoaib M, Haseeb HM, Bano K, Arshad A. Unraveling the Complexity of Immune Checkpoint Modulation in Gastrointestinal Malignancies. Pak-Euro Journal of Medical and Life Sciences. 2023;6:3.

42. Motta V, Soares F, Sun T, Philpott DJ. NOD-like receptors: versatile cytosolic sentinels. Physiological reviews. 2015 Jan;95(1):149-78.

43. Shi J, Chi S, Xue J, Yang J, Li F, Liu X. Emerging role and therapeutic implication of Wnt signaling pathways in autoimmune diseases. Journal of immunology research. 2016 Oct;2016.

44. Soria-Castro R, Schcolnik-Cabrera A, Rodríguez-López G, Campillo-Navarro M, Puebla-Osorio N, Estrada-Parra S, Estrada-García I, Chacón-Salinas R, Chávez-Blanco AD. Exploring the drug repurposing versatility of valproic acid as a multifunctional regulator of innate and adaptive immune cells. Journal of immunology research. 2019 Mar 14;2019.

45. Amadio R, Piperno GM, Benvenuti F. Self-DNA sensing by cGAS-STING and TLR9 in autoimmunity: is the cytoskeleton in control. Frontiers in Immunology. 2021 May 18;12:657344.