Journal of Advances and Scholarly Researches in Allied Education
Vol. 19, Issue No. 4, July-2022, ISSN 2230-7540

Innate Immunity in pathogenesis of Tuberculosis: An Overview

Chhangani Monika[1]*, Dr. Sushma Dubey[2]

[1] Ph.d Student, Kalinga University, Raipur

[2] Associate Professor, Department of Biotechnology, Kalinga University, Raipur

Abstract - ***An evolutionary conserved mechanism that detects and fights off illness and discomfort is the innate immune system. Through a variety of germline-encoded cell surface or cytoplasmic receptors, innate immune signalling rapidly detects infectious threats and delivers signals for the application of appropriate defences through adaptors, kinases, and transcription factors, leading to the generation of cytokines. Inflammatory reactions, which are the innate immune system's initial response to pathogenic signals, must be quick and focused in order to create a physical barrier against the spread of infection and must then be stopped once the pathogens have been eradicated.***

The human pathogen Mycobacterium tuberculosis, which largely attacks innate immune cells patrolling the lung, is what causes tuberculosis (TB). By identifying the inflammatory environment in the lungs and encouraging the development of adaptive immune responses, innate immune cells act as barometers of the immune response against Mycobacterium tuberculosisinfection. However, M. tb can easily control innate immune cells, which are also potential habitats for bacterial proliferation. Particularly in the context of human infection, our knowledge of the early interactions between M. tb and innate immune cells is restricted. This review will concentrate on innate immune pathways discovered through human immunogenic research.

Keyword - Mycobacterium tuberculosis, innate, immune, response.

----------X----------

INTRODUCTION

Mycobacterium tuberculosis (*M. tb*) is the causative agent of tuberculosis (TB), which annually results in millions of deaths worldwide. Aerosol transmission, which is helped by tissue-damaging inflammation depending on the immune system, contributes to the disease's propensity to spread widely (North and Jung, 2004). In 2019, an estimated 7.1 million new TB cases were projected. Since 2013, many nations have witnessed an increase in newly diagnosed cases. In India, the number of cases grew from 1.2 million in 2013 to 2.2 million in 2019. Despite this increase, there is still a substantial gap between the number of patients diagnosed and reported (2,9 million) and the anticipated number of TB cases in 2019 (10 million) (WHO TB Report, 2019). This discrepancy is a result of both under diagnosis and underreporting of TB cases. As governments try to bridge the gap, they report bacteriologically confirmed cases and locate them so that effective treatment may commence as soon as possible. By identifying early indicators, we have focused on the function of host cytokines in tuberculosis diagnosis.

Although one-third of the world's population is infected with *M. tb*, this infection rarely results in active illness. *M. tb* is typically transmitted through the respiratory tract, and while it can affect a range of organs, pulmonary tuberculosis (PTB) is the most common ailment it causes. Outside of the lungs is where extra-pulmonary tuberculosis (EPTB) occurs. The main issue with the disease is that the bacterium is paucibacillary, which makes it difficult to diagnose early and so delays the patient's therapy. Common signs of tuberculosis include fever, cough, lack of appetite, and weight loss; however, the majority of patients do not display these symptoms, particularly in the case of EPTB, resulting in a delay in diagnosis. In addition, specimen collection techniques are arduous and intrusive, and sample collection must be repeated if the results are negative, which is painful for the individual. Consequently, there is an immediate clinical need to create a less invasive method for TB detection.

There is always a balance between the disease burden and an individual's immunity. When this equilibrium is disturbed in a person with immunodeficiency, the disease outbreak or active disease occurs (Figure 1). Immunity of the host is

essential for the control of the disease, which results in latent TB.

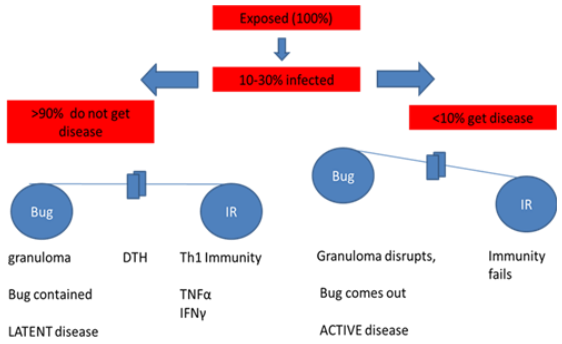

Figure 1: Mycobacterium-host immunity balance.

Mycobacterium and host immune system are in equilibrium. Due to the ubiquity of the bacterium in the air, everyone gets exposed to it. 10-30% of the individuals are infected. More than 90% of these 10-30% do not develop active disease as a result of a balance between the bacteria and their robust defence; therefore, the bug is contained in the granuloma and the individual is considered latently infected. In this stage, the insect can potentially survive his entire life without spreading disease. In less than 10% of people who contract the active illness, the bug emerges as the granuloma ruptures and is easily able to bypass the weak immunity and cause the active illness.

After infection, *M. tb* induces an innate immune response in the form of type I interferons (IFN-α/β) and IL-12. For protection, however, the TH1 branch of cell-mediated immunity is preferable, in which IL-12-primed Ag-specific CD4+ T cells generate typeII IFN, leading to the upregulation of other essential cytokines such as TNF- α (Zeng et al., 2018). In contrast to the well-established protective function of IFN-γ (type II IFN), the role of type I IFNs in bacterial infections (extracellular and intracellular) could be either detrimental or advantageous (Trinchieri et al.,2010). Type I IFNs, which consist of numerous subtypes of IFN-α and a single IFN-β, are a dedicated family of antiviral cytokines. However, in the context of tuberculosis, its role is frequently questioned because, on the one hand, IFN-α/ β can directly inhibit IL-12 and thus TH1 immunity (detrimental role) (Byrnes et al., 2001), whereas, on the other hand, it has the potential to directly induce IFNγ- from T and NK cells (TH1-promoting, protective) (Byrnes et al., 2001). (Freudenberget al., 2002). In addition, as IFN-1 inhibits the bacteriostatic activity and antigen presentation capability of *M. tb*-infected monocytes and macrophages (Bouchonnet et al., 2002), *M. tb*-infected IFNAR-/- mice outlive wild type infected animals (Manca et al., 2005). In contrast, type I IFNs have been shown to be successful in the treatment of individuals with multidrug-resistant pulmonary tuberculosis (Giouse et al., 1998; Palmero et al., 1999).

- **Biology of Interferon Type I.**

In the 1950s, interferons (IFNs) were identified as molecules rapidly produced by virus-infected cells that aid neighbouring cells in defending against viral infection (Isaacs & Lindemann, 1957). Interferon genes lack introns and so differ from those of higher species (Weismann et al., 1982). At least five kinds of IFNs exist, including alpha, beta, gamma, omega, and tau. Interferons are divided into two types: type I and type II. IFN-γ is the only type II interferon, but there are four classes of type I IFNs: IFN-α, IFN-β, IFN-Ω, and IFN-τ. There are only one Hu-IFN-α and one Hu-IFN-γ, however there are numerous IFN- species. IFN-species are the most structurally diverse, with 13 types and related polypeptides (subtypes), each expressed by a separate gene (Diaz et al., 1996). It has been found that IFN- subtypes vary in their antiviral activity and immunoregulatory properties (Foster et al., 1996). However, neither the tissue specificity nor the biological importance of the numerous IFN- subtypes are known. Individual IFN- proteins, such as human IFN-7, have varied capacities to enhance the antiviral and anti-proliferative activities of NK cells (Ortaldo et al., 1984). Given that all IFN- proteins bind to the same receptor complex; it is unknown why various IFNs have distinct effects.

Type I IFNs are not produced by a particular cell type, unlike IFN-γ, which is produced by T and NK cells. During a viral or bacterial infection, nearly every cell produces type I IFNs. It has been demonstrated that cells of epithelial, fibroblast, and hematopoietic origin produce type I IFNs in response to bacterial infection. The percentage of individual type I IFN species generated varies among cell types and tissues and is affected by the signal source for production. However, a difference should be made between cells that produce type I IFNs in minute numbers and in a confined context and those that produce enormous quantities of type I IFNs. These cells are referred to as IFN-producing cells (IPCs) and they induce a systemic response. The researchers Coccia et al. (2004) and Prakash et al (2005) IPCs are a form of plasmacytoid dendritic cell (pDC) immaturity (Cella et al., 1999; Seigal, et al., 1999).

- **Downstream Signal Transduction Pathways of Type I Interferon Receptor (IFNAR)**

Their signalling is mediated by the binding of type I interferons to the interferon alpha receptor (IFNAR). These receptors are intricately related to tyrosine kinase 2 (TYK2) and JAK1 from the Janus protein tyrosine kinase family. By binding to IFNAR chains, the ligand causes the activation of Janus kinases and the phosphorylation of tyrosine residues (R1 & 2). A phosphotyrosine-based motif generated on the receptor complex recruits STAT1 and STAT2. Janus kinases phosphorylate docked STAT protein tyrosine residues. Through the interaction of phosphotyrosine/SRC-HOMOLOGY-2 (SH2) DOMAIN, phosphorylated STAT1 and STAT2 generate two distinct transcription factors. One of the

complexes made is IFN-stimulated gene factor 3 (ISGF3), which is generated by a STAT1-STAT2 heterodimer complexed with IFN regulatory factor 9. (IRF9). ISGF3 interacts to the IFN-stimulated response element (ISRE) in the promoters of a number of type I IFN-stimulated genes (ISGs). ISGF3 appears to be the principal transcription factor responsible for ISG expression. As depicted in Figure 2, another complex generated in response to type I IFNs is composed of STAT1 homodimers that bind a different promoter sequence, gamma IFN-activated site (GAS). STAT1 homodimers are also produced downstream of IFNR signalling, which is well-known for its ability to coordinate transcriptional responses to IFN-γ, although their significance in type I IFN signalling remains unknown (Decker et al., 2005).

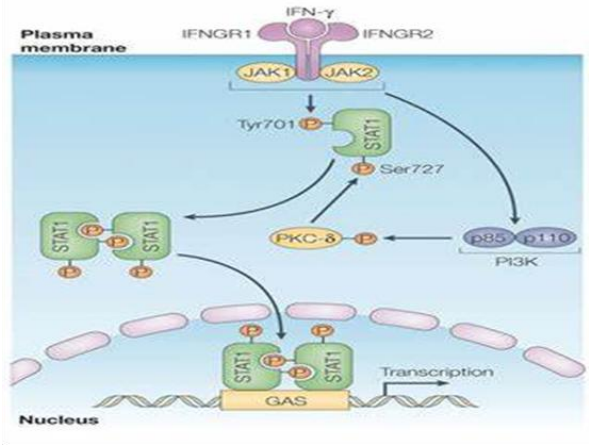

Figure 2: Interferon (IFN) receptors' signalling processes.*Source: Decker et.al., 2005*

- **Signal Transduction to IFN genes of Type I**

Activation of the transcription factors IRF3 and IRF7 is a defining characteristic of type I IFN mediated signal transduction (Honda et al., 2005; Taniguchi et al., 2002). IRF3 is probably expressed in all cells constitutively and in response to viral and bacterial pathogen infection. It is phosphorylated on serine residues by one of two IB-kinase-related kinases: tank-binding kinase 1 (TBK1) and IKK-i (Sharma et al., 2003). (Figure 3).

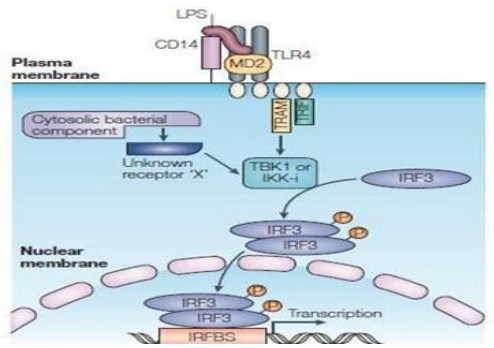

Figure 3: Different receptors induce type I IFNs in cytosolic and extracellular bacteria

Phosphorylated and dimerized IRF3 forms with NF-B, activator protein 1 (AP1) family members, and high-mobility group (HMG) proteins, which binds the IFN promoter and, in some instances, the IFN4 promoter, thereby enhancing the production of type I IFN genes (Thanos et al., 1995;Sato et al., 2000). Intracellular pathogens, such as viruses and some facultative intracellular bacteria, can be identified via cell-surface immunoreceptors, endosome/phagosome-based membrane-bound immunoreceptors, and cytoplasmic pathogen sensors. These pathogen recognition mechanisms, which may either originate on the outside or inside of cells, activate IRF3 and IRF7, leading to the generation of type I IFNs.

Amplification of the type I IFN Response TLR or cytoplasmic recognition of bacteria triggers the IRF3 pathway, which is related to the activation of IFN- and/or IFN-4 (Mariéet al., 1998). IRF7 activation is required for the expression of the other genes and is more prevalent during viral and bacterial infections (Sato et al., 2000; Marié et al., 1998; Sato et al., 1998). IRF7 is activated by the repeated phosphorylation of serine nucleotides by the TBK1 and IKK-i kinases, which function downstream of TLR3 and TLR4 (Sharma et al. 2003, Sato et al. 1998). All cells, excluding IPCs, use an IRF7-based 'amplification loop' to increase type I IFN production (Levy et al., 2003) (Figure 4).

If pathogen recognition signals and TBK/IKK-i activity continue to this step, newly generated IRF7 is phosphorylated and all types of IFN genes are transcribed. In contrast, IPCs have always utilized an IRF7 activation method that is intermediate between TLR7 and TLR9 and fundamentally independent of TLR3 and TLR4. TLR7 and TLR9 recognize single-stranded RNA and non-methylated CPG DNA, respectively, from bacteria, and ligand binding causes fast activation of IRF7 and large levels of IFN- in human cells TBK1 or IKK-i28 (Honda et al., 2004; Uematsu et al., 2005). The assembly of MyD88 adaptors is triggered by ligand recognition, TRAF6, serine/threonine kinases, and IRAK4 (Honda et al., 2004). (Figure 4). IRAK1 may interact directly with IRF7 in vitro and phosphorylate it (Uematsu et al., 2005). IFN-production by L. monocytogenes-infected macrophages is fully dependent on early IFN-synthesis (Stockingeret al., 2004). Type I IFN production was amplified in human dendritic cells infected with Mycobacterium tuberculosis (Remoli et al., 2002).

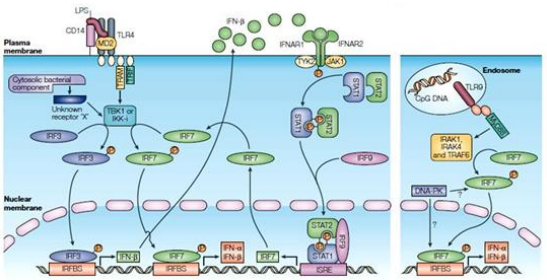

Figure 4: Bacterial stimulation of interferon (IFN) regulatory factor 7

- **Interaction between Type I and Type II Interferons**

IFN-γ is a more effective stimulator of phagocytic cell and antigen-presenting cell function than type I IFN. The complex interaction between type I and type II IFN signals has received little study. During the same immune response, both types of IFNs are frequently produced, and data suggests that cross-regulation has physiologically significant effects (Figure 5). IFN produced by fibroblasts inhibits IFN-induced transcription of genes in activated macrophages (Ling et al., 1985). Exposure of human macrophages in vitro to type I IFNs decreases IFN-γ binding to cells, hence inhibiting the development of class II MHC, Fc receptor, and oxidative burst generation (Ling et al., 1985; Yoshida et al., 1988).

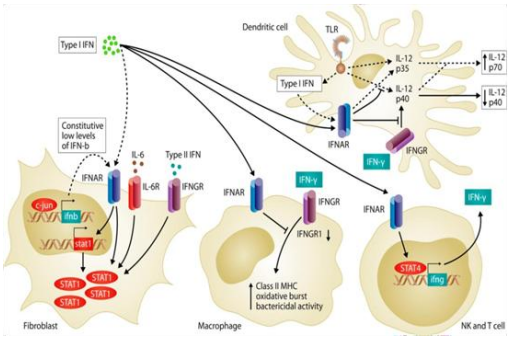

Figure 5: depicts the interaction between typeI IFN and IFN-γ.

In mice infected with Listeria monocytogenes, type I interferon (IFN-1) has been shown to downregulate IFN- receptor (IFNR) expression on macrophages and dendritic cells, hence decreasing the responsiveness to IFN-γ during systemic infection (Rayamajhi et al., 2010). Because type I IFN can activate STAT1 homodimers, it can duplicate the IFN-γ gene induction pattern (Boxel-Dezaire et al., 2006). In addition, cells are continuously exposed to low quantities of type I IFN, and the consequent weak signal is required for the cells to produce significant levels of IFN in response to inducing stimuli (Taniguchi and Takaoka, 2001). Type I IFNs inhibit IL-12 production by human monocytes/macrophages. A decrease in PU.1 binding activity at the IL-12p40 promoter's upstream Ets site is evidence of transcriptional repression of the IL-12p40 gene (Byrnes et al., 2001). Type I IFNs have been shown to be able to substitute for IL-12 in boosting IFN- production from T and NK cells (Brinkmann et al., 1993; Freudenberg etal., 2002; Nguyen et al., 2000).

- **Negative Regulation of IFN Signaling of Type I**

Multiple mechanisms, including SHP-1 and SHP-2 dephosphorylation (Yetter et al., 1995; You etal., 1999), have been implicated in the termination of IFN-signalling(tenHoeve et al., 2002). Tyk2 was also shown to regulate and stabilize IFNAR1 expression (Ragimbeau et al., 2003).

Several cytokine-stimulated pathways are inhibited by the suppressor of cytokine signalling (SOCS) protein family (also known as STAT induced STAT inhibitor (SSI), cytokine inducible SH2-containing protein (CIS), or JAK binding protein (JAB)) (Alexander et al., 2004).

- **Why Interferon Type I?**

Interferons of type I are potent antiviral immune-modulators that protect against the vast majority of viral infections. Initial most of infections promote the formation of type I IFN and a normal immune response. Numerous studies have demonstrated that type I IFNs have both beneficial and detrimental effects on bacterial infections.

- **Bacterial infections and type I IFN.**

While type II IFN (IFN-γ) is well known for its antibacterial response, type I IFNs (IFN- α and IFN-β) are well known for their antiviral reaction (Muller et al., 1994; Dalton et al., 1993; van den Broek et al., 1995). The study of type I IFNs' role in bacterial infection, however, is still in its early phases. The mouse becomes more susceptible to bacterial infection when exposed to type I IFN, which has been shown to sensitize lymphocytes to apoptosis in Listeria infection (Carrero, 2004). Human lymphocytes' IFN-production is stimulated by Staphylococcus aureus protein A. (Smith et al., 1983). Additionally, type I IFNs have been discovered to shield mice from Listeria infection by increasing IFN- production separately from IL-12 (Freudenberg et al., 2002). One study found that a second bacterial-derived stimulation, such as LPS, lipoteichoic acid, or TNF- plus PGE2, destroyed immature monocyte-derived DCs that had received IFN- treatment. It has also been shown that IFN- and GM-CSF cytokines produced dendritic cells with stronger functional activity than dendritic cells cultured with IL-4/GM-CSF, contradicting the aforementioned finding and indicating that DC creation with GM-CSF in the absence of IL-4 is viable (Santini et al., 2000; Paquette et al., 1998). IFN produced by NK cells through IFN stimulation by macrophages in Salmonella infection kills the bug (Owen et al., 2016).

- **Type I IFN during mycobacterial infection**

One of the distinguishing features of innate immune responses to *M. tb* is the signalling through innate immunity receptors by dendritic cells to release cytokines such as type I IFN (IFN-α/β), which improves priming of CD8+ T cell responses (Remoli et al., 2002). Neutrophil reduction was associated with an increase in *M. Bovis* BCG growth in vivo, demonstrating that neutrophils also play a protective role in TB immunity (Fulton et al., 2002). Unmethylated mycobacterial DNA has been shown

to be immune-stimulatory due to TLR9 identification of unmethylated CpG sequences (Tokunaga et al., 1984); subsequent TLR9 signalling creates IFN-α/β and other cytokines. Additionally, type I interferon responses and the detection of *M. tb* molecular patterns have been linked to cytosolic receptors (Pandey et al., 2009). TLR9-induced IFN-α/β enhances bystander T lymphocyte cross priming and phenotypic development in vivo (Kamath et al., 2005). IFN-α/β has been shown to activate cytolytic CD8+ T cells in mice and stimulate cross-processing in dendritic cells (DCs) in response to CpG DNA (Datta et al., 2003). According to research by Bafica et al. (2005), mice lacking in both TLR2 and TLR9 are more susceptible to M. tb infection than either single deletion. This finding suggests that TLR2 and TLR9 work together to protect the host against *M. tb*. By binding to DNA and inducing cellular and humoral responses, most likely via a TLR9 dependent pathway, a DNA binding protein (orthologous to MDP1) may operate as an immune-dominant antigen, resulting in the generation of pro-inflammatory cytokines and the stimulation of IFN- production (Hemmi et al., 2000; Prabhakar et al., 1998).

In response to several encapsulated viruses, bacteria, and DNA with unmethylated CpG sequences, pDCs produce type I IFN (Kadowaki et al., 2000; Fitzgerald et al., 2002). The differences in DC subsets in TB patients are a topic of discussion. PTB and extra-pulmonary TB patients had higher levels of circulating pDCs than healthy controls (Mendelson et al., 2006). These results were similar to those of another study, which found that patients with untreated acid-fast bacilli (AFB) had more pDCs and less mDCs compared to healthy family contacts (Gupta et al., 2010). Similar mDC declines have been seen in other cases (Uehira et al., 2002). They demonstrated that the buildup of mDCs in tuberculous granulomas was the reason for the decrease in mDCs. In contrast, TB patients had a lower overall number of DC subtypes (both mDCs and pDCs) (Lichtner et al., 2006). However, they combined individuals with pulmonary and extra pulmonary tuberculosis. In contrast to the study (Gupta et al., 2010), which used HFCs clinically free of TB as controls for comparison analysis, both studies' controls (Mendelson et al., 2006; Lichtner et al., 2006) were healthy blood donors. In addition to changing during infection, DC subsets have been shown to recover and restore their ratio among subsets after receiving appropriate treatment in TB patients (Lichtner et al., 2006; Gupta et al., 2010).

The whole bacterium-based SELEX method was used to identify *Shigellasonne, Mycobacterium tuberculosis, pathogenic strains of Staphylococcus aureus, Lactobacillus acidophilus, E. coli*, and *Lactobacillus acidophilus* (Hamula et al., 2008). (Masoudipour et al., 2011).

CONCLUSION

The interaction between *M. tuberculosis* and the human host affects how an infection turns out. Both innate and adaptive defensive systems are implicated with regard to the human host. Numerous outcomes could occur following *M. tuberculosis* uptake in alveolar macrophages. If M. tuberculosis is eliminated right away, no adaptive T-cell response will be produced. But after an infection has taken hold, a localised, non-specific inflammatory response develops. A network of pro- and anti-inflammatory cytokines and chemokines controls this response. At this time, dendritic cells or macrophages produce the majority of the mediators, but IFN- -γ has a variety of cellular origins, including NK cells, T cells, and CD1-restricted T cells. This early response affects whether the infection is contained or spreads locally by M. tuberculosis (sometimes). *M. tuberculosis* has created strategies to work around or counteract protective immunity at numerous points throughout the host response.

The effectiveness of several innate host defensive mechanisms may help to partially explain the inter-individual variations in outcome following *M. tuberculosis* infection. Innate immunity may be influenced by phagocytosis, immunological recognition, cytokine generation, and effector pathways.

REFERENCES

1. Alexander, W.S. and Hilton, D.J. 2004.The role of suppressors of cytokine signaling (SOCS) proteins in regulation of the immune response. Annu RevImmunol, 22, 503-529
2. Bafica, A., Scanga, C. A., Feng, C. G., Leifer, C., Cheever, A., and Sher, A. 2005. TLR9 regulates Th1 responses and cooperates with TLR2 in mediating optimal resistance to Mycobacterium tuberculosis. J Exp Med, 202 (12), 1715-1724
3. Bouchonnet, F., Boechat, N., Bonay, M. and Hance, A. J. 2002 Alpha/beta interferon impairs the ability of human macrophages to control growth of Mycobacterium bovis BCG. Infect Immun, 70 (6), 3020-3025
4. Brinkmann, V., Geiger, T., Alkan, S., and Heusser, C. H. 1993. Interferon alpha increases the frequency of interferon gamma-producing human CD4+ T cells. J Exp Med, 178 (5), 1655-1663.
5. Carrero, J. A., Calderon, B., and Unanue, E. R. 2004. Type I interferon sensitizes lymphocytes to apoptosis and reduces resistance to Listeria infection. J Exp Med, 200(4), 535-540.
6. Cella, M., Jarrossay, D., Facchetti, F., Alebardi, O., Nakajima, H., Lanzavecchia, A., et al. 1999. Plasmacytoid monocytes migrate to inflamed lymph nodes and produce large amounts of type I interferon. Nat Med, 5 (8), 919-923.
7. Datta, S.K., Redecke, V, Prilliman, K.R., Takabayashi, K., Corr, M., Tallant, T., et al. et al., 2003.A Subset of Toll-Like Receptor Ligands Induces Cross presentation by Bone Marrow-Derived Dendritic Cells.J Immunol, 170(8), 4102 -4110.

8. Decker, T., Müller, M. & Stockinger, S. 2005. The yin and yang of type I interferon activity in bacterial infection. Nat Rev Immunol, 5 (9), 675-687.
9. Diaz, M.O., Bohlander, S. and Allen, G. 1996.Nomenclature of the human interferon genes.J Interferon Cytokine Res, 16(2),179-180.
10. Fitzgerald-Bocarsly, P. 2002. Natural interferon-alpha producing cells: the plasmacytoid dendritic cells. BioTechniques, 22, 24-29.
11. Foster, G. R., Rodrigues, O., Ghouze, F., Schulte-Frohlinde, E., Testa, D., Liao, M. J., et al. 1996. Different relative activities of human cell-derived interferon alpha subtypes: IFN-alpha 8 has very high antiviral potency. J Interferon Cytokine Res, 16 (12), 1027-1033.
12. Freudenberg, M.A., Merlin TG., Kalis T., Chvatchko Y., Stubig H. and Galanos C. 2002. Cutting edge: a murine, IL-12-independent pathway of IFN-gamma induction by gram-negative bacteria based on STAT4 activation by Type I IFN and IL-18 signaling. J Immunol, 169(4),1665-1668.
13. Fulton, S.A., Reba, S., Martin, T. D., and Boom, W. H. 2002.Neutrophil-mediated mycobacteriocidal immunity in the lung during Mycobacterium bovis BCG infection in C57BL/6 mice.Infect Immun, 70(9),5322-5327.
14. Giosue, S., Casarini, M., Alemanno, L., Galluccio, G., Mattia, P., Pedicelli, G., et al. 1998.Effects of aerosolized interferon-alpha in patients with pulmonary tuberculosis.Am J Respir Crit Care Med, 158 (4), 1156-1162.
15. Gupta, V., Jaiswal, A., Behera, D., and Prasad, H. K. 2010. Disparity in circulating peripheral blood dendritic cell subsets and cytokine profile of pulmonary tuberculosis patients compared with healthy family contacts. Hum Immunol, 71(7), 682-691.
16. Hamula, C.L., Zhang, H., Guan, L.L., Li, X.F., and Le, X.C. 2008.Selection of aptamers against live bacterial cells.Anal Chem, 80 (20), 7812-7819.
17. Hemmi, H., Takeuchi, O., Kawai, T., Kaisho, T., Sato, S., Sanjo, H., et al. 2000. A Toll-like receptor recognizes bacterial DNA. Nature, 408 (6813), 740-745.
18. Honda, K., Yanai, H., Negishi, H., Asagiri, M., Sato, M., Mizutani, T., et al. 2005. IRF-7 is the master regulator of type-I interferon-dependent immune responses. Nature, 434 (7034), 772-777.
19. Isaacs, A., &Lindenmann, J. 1957. Virus Interference. I. The Interferon. Proc. Royal Soc. B: Biological Sciences, 147(927), 258–267.
20. Kamath, A.T., Sheasby, C.E. and Tough, D.F. 2005.Dendritic Cells and NK Cells Stimulate Bystander T Cell Activation in Response to TLR Agonists through Secretion of IFN-αβ and IFN-γ.J Immunol, 174(2), 767 -776.
21. Lee, C. K., Raz, R., Gimeno, R., Gertner, R., Wistinghausen, B., Takeshita, K., et al. 2002. STAT3 is a negative regulator of granulopoiesis but is not required for G-CSF-dependent differentiation. Immunity, 17 (1), 63-72.
22. Levy, D.E., Marié, I. and Prakash, A. 2003.Ringing the interferon alarm: differential regulation of gene expression at the interface between innate and adaptive immunity.CurrOpin Immunol, 15(1), 52-58.
23. Lichtner, M., Rossi, R., Mengoni, F., Vignoli, S., Colacchia, B., Massetti, A. P., et al.2006. Circulating dendritic cells and interferon-alpha production in patients with tuberculosis: correlation with clinical outcome and treatment response.Clin Exp Immunol, 143 (2), 329-337.
24. Ling, P.D., Warren, M.K. and Vogel, S.N.1985. Antagonistic effect of interferon-beta on the interferon-gamma-induced expression of Ia antigen in murine macrophages. J Immunol, 135(3),1857-1863
25. Manca, C., Tsenova, L., Freeman, S., Barczak, A. K., Tovey, M., Murray, P. J., et al. 2005. Hypervirulent M. tuberculosis W/Beijing strains upregulate type I IFNs and increase expression of negative regulators of the Jak-Stat pathway. J Interferon Cytokine Res, 25 (11), 694-701.
26. Mariotti, S., Teloni, R., Iona, E., Fattorini, L., Romagnoli, G.,Gagliardi, M. C., et al.2004. Mycobacterium tuberculosis Diverts Alpha Interferon-Induced Monocyte Differentiation from Dendritic Cells into Immunoprivileged Macrophage-Like Host Cells.Infect. Immun., 72(8), 4385-4392.
27. Masoudipour, E., Mousavi, S.L., and Basiri, M. 2011. Specific detection of Shigella sonnei by enzyme-linked aptamer sedimentation assay.Prog Biol Sci, 1 (1), 11-15.
28. Mendelson, M., Hanekom, W.A., Ntutela, S., Vogt, M., Steyn, L., Maartens, G., et al. 2006. Quantitative and functional differences between peripheral blood myeloid dendritic cells from patients with pleural and parenchymal lung tuberculosis. ClinVaccine Immunol: CVI, 13(12),1299-1306.
29. Muller, U., Steinhoff, U., Reis, L. F., Hemmi, S., Pavlovic, J., Zinkernagel, R. M., et al. 1994.Functional role of type I and type II interferons in antiviral defense.Science, 264 (5167), 1918-1921.
30. North, R.J. & Jung, Y., 2004.Immunity to tuberculosis.Annu. Rev. Immunol, 22, 599- 623.
31. Ortaldo, J. R., Herberman, R. B., Harvey, C., Osheroff, P., Pan, Y. C., Kelder, B., et al. 1984. A species of human alpha interferon that lacks the ability to boost human natural killer activity.Proc Natl Acad Sci U S A, 81 (15), 4926-4929.
32. Palmero, D., Eiguchi, K., Rendo, P., Castro Zorrilla, L., Abbate, E., and Gonzalez Montaner, L. J. 1999. Phase II trial of recombinant interferon-alpha2b in patients with advanced intractable multidrug-resistant pulmonary tuberculosis: long-term follow-up. Int J Tuberc Lung Dis, 3 (3), 214-218.
33. Pandey, A. K., Yang, Y., Jiang, Z., Fortune, S. M., Coulombe, F., Behr, M. A., et al. 2009. NOD2, RIP2 and IRF5 play a critical role in the type I interferon response to Mycobacterium tuberculosis. PLoSPathog, 5 (7), e1000500.

34. Prabhakar, S., Qiao, Y., Hoshino, Y., Weiden, M., Canova, A., Giacomini, E. et al. 2003 Inhibition of response to alpha interferon by Mycobacterium tuberculosis.Infect Immun, 71 (5), 2487-2497.
35. Ragimbeau, J., Dondi, E., Alcover, A., Eid, P., Uze, G., and Pellegrini, S. 2003. The tyrosine kinase Tyk2 controls IFNAR1 cell surface expression. Embo J,22 (3), 537-547.
36. Rayamajhi, M., Humann, J., Penheiter, K., Andreasen, K., and Lenz, L. L. 2010. Induction of IFN-alphabeta enables Listeria monocytogenes to suppress macrophage activation by IFN-gamma. J Exp Med 207 (2), 327-337.
37. Remoli, M. E., Giacomini, E., Lutfalla, G., Dondi, E., Orefici, G., Battistini, A., et al. 2002. Selective expression of type I IFN genes in human dendritic cells infected with Mycobacterium tuberculosis. J Immunol, 169 (1), 366-374.
38. Sato, M., Hata, N., Asagiri, M., Nakaya, T., Taniguchi, T., Tanaka, N. 1998.Positive feedback regulation of type I IFN genes by the IFN-inducible transcription factor IRF-7.FEBS Letters, 441(1), 106-110.
39. Sharma, S., teneOver, B., Grandvoux, N., Zhou, G P., Lin, R., and Hiscott, R. 2003. Triggering the interferon antiviral response through an IKK-related pathway. Science (New York, N.Y.), 300 (5622), 1148-1151.
40. Siegal, F. P., Kadowaki, N., Shodell, M., Fitzgerald-Bocarsly, P. A., Shah, K., Ho, S., et al. 1999.The nature of the principal type 1 interferon-producing cells in human blood.Science, 284 (5421), 1835-1837.
41. Stockinger, S., Reutterer, B., Schaljo, B., Schellack, C., Brunner, S., Materna, T., et al. 2004. IFN regulatory factor 3-dependent induction of type I IFNs by intracellular bacteria is mediated by a TLR- and Nod2-independent mechanism. J Immunol,173(12), 7416-7425.
42. Taniguchi, T. and Takaoka, A. 2001. A weak signal for strong responses: interferon-alpha/beta revisited. Nat Rev Mol Cell Biol, 2 (5), 378-386.
43. Taniguchi, T. and Takaoka, A. 2002. The interferon-alpha/beta system in antiviral responses: a multimodal machinery of gene regulation by the IRF family of transcription factors. CurrOpin Immunol, 14(1), 111-116.
44. ten Hoeve, J., de Jesus Ibarra-Sanchez, M., Fu, Y., Zhu, W., Tremblay, M., David, M., et al. 2002. Identification of a nuclear Stat1 protein tyrosine phosphatase.Mol Cell Biol, 22 (16), 5662-5668.
45. Thanos, D. and Maniatis, T. 1995. Virus induction of human IFN beta gene expression requires the assembly of an enhanceosome. Cell, 83(7), 1091-1100.
46. Tokunaga, T., Yamamoto, H., Shimada, S., Abe, H., Fukuda, T., and Fujisawa, Y. 1984. Antitumor activity of deoxyribonucleic acid fraction from Mycobacterium bovis BCG. I. Isolation, physicochemical characterization, and antitumor activity. JNatl Cancer Inst, 72(4), 955-962.
47. Trinchieri, G., 2010. Type I interferon: friend or foe? J Exp Med 207, (10), 2053- 2063.
48. Uehira, K., Amakawa, R., Ito, T., Tajima, K., Naitoh, S., Ozaki, Y., et al. 2002. Dendritic cells are decreased in blood and accumulated in granuloma in tuberculosis. Clin Immunol,105 (3), 296-303.
49. Uematsu, S., Sato, S., Yamamoto, M., Hirotani, T., Kato, H., Takeshita, F., et al.2005. Interleukin-1 receptor-associated kinase-1 plays an essential role for Toll-like receptor (TLR)7- and TLR9-mediated interferon-{alpha} induction. J Exp Med, 201 (6), 915-923.
50. Weismann, C., Nagata, S., Boll, S., Fountoulakis, M., Fujisawa, A., Fujisawa, J., et al. 1982.Structure and expression of human alpha-interferon genes.Princess Takamatsu Symp, 12, 1-22.
51. World Health Organization. 2019. Global tuberculosis report 2019. World Health Organization. https://apps.who.int/iris/handle/10665/329368
52. Yetter, A., Uddin, S., Krolewski, J.J., Jiao, H., Yi, T., and Platanias, L. C.1995.Association of the interferon-dependent tyrosine kinase Tyk-2 with the hematopoietic cell phosphatase.J Biol Chem, 270(31),18179-18182.
53. You, M., Yu, D.H. and Feng, G.S. 1999. Shp-2 tyrosine phosphatase functions as a negative regulator of the interferon-stimulated Jak/STAT pathway. Mol Cell Biol, 19(3),2416-2424.
54. Zeng, G., Zhang, G. and Chen, X., 2018.Th1 cytokines, true functional signatures for protective immunity against TB?*Cell Mol Immunol* 15(3), 206-215.

Corresponding Author

Chhangani Monika*

Ph.d Student, Kalinga University, Raipur