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TNF-α and its Role in Tuberculosis

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ABSTRACT

Tuberculosis (TB) is an infectious disease caused by intracellular pathogen *Mycobacterium tuberculosis* which stands as an important public health problem. It was declared as a global health emergency by WHO in 1993 and it was for the first time when an infectious disease got such crooked distinction. TB causes about 1.5 million deaths every year and nearly one-third of the world population is infected with *M. tuberculosis*. Immune action against TB involves a cytokine mediated complex interplay of innate and adaptive immune system. TNF-α is a proinflammatory cytokine which functions in pathogenesis of TB by helping in granuloma formation, macrophage activation, Dendritic cell maturation and apoptosis of *M. tuberculosis* infected cells. This review aims to highlight the pivotal role of TNF-α in controlling the *Mycobacterium* infection and describes the current knowledge of TNF-α signaling.

1. Introduction

TB is an infectious, granulomatous disease caused by *M. tuberculosis* which causes harm to life globally (Lindenau *et al*., 2014). *M. tuberculosis* belongs to a family of bacteria known as *Mycobacterium tuberculosis complex (MTBC)* which also includes other TB causing pathogens of the genus *Mycobacteria* which is presumed to be originated about 150 million years ago and most modern members of MTBC complex originated about 15,000-30,000 years ago (Nicklisch *et al*., 2012). Neolithic age harbours the earliest known cases of TB as in Atlit-Yam (Isarel, Asia), the major Mediterranean submerged site provides three evidences of the disease. Europe faced TB epidemic in beginning of 17th century which later invaded America and Africa (Bates and Stead, 1993; Palomino *et al.,* 2007). In 1882, Robert Koch obtained pure cultures of *M. tuberculosis* from infected human and animal tissues and proved that it was always present in TB infections (Koch 1982; Barnes, 2000; Porth 2002; Knechel, 2009).

Consequences of TB display massive impact on society by hindering its socioeconomic development as maximum cases of TB occur between age of 15-54 which is considered as the most productive age group. Its devastating effects are clear from the statistics provided by WHO Global Tuberculosis Report 2017 which states that TB stands as 9th leading cause of death globally as it killed almost 1.3 million HIV negative TB patients and 0.37 million HIV positive TB patients in year 2016 (WHO, 2017). India bears one-fourth of global TB burden and holds second highest number of HIV associated TB globally. It accounts for an estimated of 26% global deaths among combined HIV negative and HIV positive TB patients. Because of the continuous efforts of revised national tuberculosis control programme (RNTCP) incidence rate of TB in India decreased from 289 per 1,00,000 people in 2000 to 217 per 1,00,000 people in 2015 and mortality rate decreased from 56 per 1,00,000 people in 2000 to 36 per 1,00,000 people in 2015 (RNTCP, 2017; WHO, 2017).

The present study reviews the current knowledge of innate and adaptive immune mechanisms in pathogenesis of TB with a focus on role of pro-inflammatory cytokine TNF-α in it. It also talks about TNF-α signaling through its receptors TNFR1 and TNFR2 present over immune cells and effect of TNF-α inhibitors in a patient with *M. tuberculosis* infection.

2. Pathogenesis of TB

An individual with active infectious TB adds aerosol droplets containing *M. tuberculosis* to air by coughing, sneezing, spitting and speaking etc. which upon inhalation enters into respiratory tract of a healthy individual and by evading its mucociliary system they reach lung alveoli. In lung alveoli *M. tuberculosis* is phagocytosed by alveolar macrophages (AMs) which release proteolytic enzymes and cytokines to kill them and these released cytokines also recruit other cells such as T lymphocytes, monocytes and neutrophils. Accumulation of macrophages, neutrophils and T lymphocytes lead to formation of nodular lesions called as granulomas which restrict the spread of M. *tuberculosis* and lead to development of a localized primary TB infection. Macrophages present in centre of lesion are destroyed leading to formation of caseous necrosis and in a person with strong immune system these lesions undergo fibrosis and calcification which results in successful control of infection and thus to latent form of TB. On the other hand in people with lesser effective immune system liquefaction of necrotic tissue occurs and walls of granuloma break draining *M. tuberculosis* containing semi-liquid matter into bronchus, blood and lymphatic vessels which happens in about 5-10% of cases and is called as the active form of TB (Knechel, 2009; Zuniga *et al*., 2012).

3. Immunity against TB

Immune action against TB involves a complex interplay of both innate and adaptive immune system. Innate immunity involves the cytokine mediated action of immune cells such as monocytes, neutrophils, Dendritic cells (DCs) and Natural killer (NK) cells and adaptive immunity involves T cell mediated immunity and B cell mediated humoral mmunity (Gupta *et al*., 2012).

Innate immunity

AMs upon engulfment of *M. tuberculosis* produce anti-bacterial molecules, reactive oxygen intermediates (ROI) and reactive nitrogen intermediates (RNI) and *Mycobacterium* which evade this bactericidal activity proliferate and induce AMs to produce pro-inflammatory cytokines such as TNF-α, IL-6, IL-12, IL-8, IL-18, IL-1α and IL-1β which recruits other immune cells such as monocytes, neutrophils, Dendritic cells (DCs) and Natural killer (NK) cells at the site of infection (Sadek *et al*., 1998; Ahmad, 2011). These immune cells form an important component of innate immunity against M. tuberculosis (Gupta *et al*., 2012). Neutrophils are the first cells to be recruited at this site by IL-8 released from AMs and carry out the phagocytosis of *M. tuberculosis* (Sawant and McMurray 2007). Monocytes are recruited at site of infection by chemokines secreted from AMs where they get differentiated into tissue macrophages having the potential of phagocytosis. Activation of tissue macrophages is done by IFN-γ secreted from T lymphocytes and NK cells and this interaction between IFN-γ releasing T lymphocytes and tissue macrophages is most critical process for control of *M. tuberculosis* infection because T cell activated tissue macrophages are the most powerful effector cells against *M. tuberculosis* (Vankayalapati and Barnes, 2009; Abbas and Lichtman, 2014).

Cytokines in immunity against TB infection

Cytokines produced by immune cells involved in immunity against TB are grouped into pro-inflammatory and anti-inflammatory cytokines. Pro-inflammatory cytokines which are TNF-α, IFN-γ, Interleukin-1 (IL-1), IL-6, IL-18 and granulocyte macrophage colony stimulating factor (GM-CSF) are mainly produced by helper T cells and macrophages. TNF-α facilitates the control of *M. tuberculosis* infection by helping in granuloma formation, macrophage activation and chemokines induction. IFN-γ activates tissue macrophages and induces the production of ROI and RNI in them, promotes cell proliferation, adhesion and apoptosis. One specific action of IFN-γ includes upregulation of antigen presentation through induced expression of class I and II major histocompatibility complex (MHC) molecules on surface of macrophages and T lymphocytes which in turn increases the visibility of pathogen to the host (Schoenborn and Wilson, 2007). IL-6 is important in T and B lymphocyte response development and its absence affects IFN-γ response and thus causes slight increase in *M. tuberculosis* burden (Saunders *et al*., 2004). IL-23 plays role in Th1 and Th17 polarisation, IL-12 in Th1 polarisation and IL-17 plays role in macrophage activation, recruitment of neutrophils and granuloma formation (Khader *et al*., 2010, 2011; Etna *et al*., 2014). Anti inflammatory cytokines which are IL-4, IL-6, IL-10, IL-11 and IL-13 are regulatory cytokines which act with certain cytokine inhibitors and cytokine receptors to regulate immune response. They are quite helpful in conditions involving excess inflammation but at times they may create susceptibility of the individual to infectious diseases like TB by over inhibiting immune response (Kasai *et al*., 1997; Opal and DePalo, 2000).

T cell mediated immunity

T cells are activated in peripheral lymphoid organ by antigen presentation on MHC Class II molecule of DCs. CD4+ T cells on antigen recognition leads to production of certain pro-inflammatory and anti-inflammatory cytokines such as IL-6, IL-21, IL-1β, IL-12, IL-23 and TGF-β. Th1 cells produce IFN-γ, IL-2 and IL-12 and Th17 cells produce IL-17, IL-21 and IL-22 as their signature cytokines. IL-17 is the chief cytokine needed for granuloma formation because it promotes initial neutophil recruitment during infection (Torrado and Cooper *et al*., 2010). After activation T cells are guided out of lymph nodes by chemokine gradients and they release IFN-γ which activates bactericidal mechanism of infected macrophages and TNF-α which stimulates apoptosis of infected cells and also helps in granuloma formation and maintenance. CD8+ cells recognize antigens presented by MHC Class I molecules and are also involved in production of TNF-α and IFN-γ in some amount (Gupta *et al*., 2012). Both CD8+ T cells and γδT cells carry out cytolysis of *M. tuberculosis* infected cells by releasing granzymes and perforins. This cytolytic activity by CD8+ T cells could be carried out in a Fas ligand dependent or independent mechanism (Zuniga *et al*., 2012; Barber and Barber, 2015).

B cell mediated immunity

Humoral response through B cell released antibodies was frequently assumed to be unprotective because of the intracellular location of *M. tuberculosis* but certain studies which were carried out using monoclonal antibodies against *M. tuberculosis* antigens such as acrystallin and MPB83 have revealed significant effects in controlling the infection to higher levels (Williams *et al*., 2004). These antibodies are supposed to act by interferring the mechanisms through which *M. tuberculosis* invades itself such as complement system activation, *M. tuberculosis* toxin neutralization and promoting fusion of phagosome and lysosome (Gupta *et al*., 2012).

4. TNF-α: Gene Structure and protein characters

TNF-α is a pleiotropic pro-inflammatory cytokine which is predominantly produced by monocytes/macrophages and other immune cells such as DCs, T cells and B cells and is involved in immune response and pathogenesis of several diseases (Varfolomeev *et al*., 2008; Quesniaux *et al*., 2010). It was discovered as a factor produced by macrophages when they are stimulated with endotoxin which can cause haemorrhagic necrosis of transplanted tumour and later on it was identified and described by Dr. G. Granger as a soluble cytotoxic factor produced by macrophages (Mootoo *et al*., 2009). It exists in both soluble and trans-membrane form having latter as its pre-dominant form. It is synthesized as a type II trans-membrane trimeric protein of 212 amino acids which is present bound to the membrane and its soluble form is generated upon cleavage of its trans-membrane form by tumour necrosis factor-alpha converting enzyme (TACE) (Black *et al*., 1997; Moss *et al*., 1997). *TNF-α* gene is located on chromosome no. 6 in class III region of major histocompatibility complex (MHC) and is of approximately 3 kb in size and contains 4 exons and 3 introns. The primary transcript formed from TNF-α gene transcription is of 2038 bp which is spliced and processed to form a fully functional mRNA of approximately 1672 bp. This mRNA upon translation forms a protein of 233 amino acids which is monomeric and non-glycosylated (Pennica *et al*., 1984; Nedwin *et al*., 1985).

5. TNF-α receptor and signaling

Two type of receptor are present for binding TNF-α which are TNFRp55 (also called TNFR1; CD120a; p55/60) having

ubiquitous expression and TNFRp75 (also called TNFR2; CD120b; p75/80) which is expressed only by immune cells. These receptors are trimeric and exist in both soluble and trans-membrane form requiring the proteolytic catalytic cleavage activity of TACE for their interconversion (Peschon *et al*., 1998; Reddy *et al*., 2000).

Extracellular part of both receptors consists of 4 homologous cysteine rich domain (CRD) which is a hallmark of TNF super-family. Intra-cellular domain (ICD) of TNFR1 has Death Domain (DD) which is an 80 amino acid sequence that allows it to associate with other DD containing proteins and TNFR2 does not have DD and interacts with other proteins via TNF Receptor Associated Factor (TRAF) binding site (Sessler *et al*., 2013). Both of these receptors involve signalling by activating NF-κB and MAP kinase but the biochemical activities carried out by them are different. Due to the presence of DD TNFR1 is involved in apoptotic and necroptotic cell death pathways whereas due to the absence of DD TNFR2 carries out mainly proliferative activities and is only sometimes involved in apoptotic pathways (Varfolomeev and Vucic, 2018).

6. TNFR1 signalling

TNFR1 signalling is initiated by binding of trimeric form of TNF-α to TNFR1 which causes conformational changes in it allowing adaptor molecule TRADD (TNFR1 associated DD protein) to come and bind with DD of receptor and it enables recruitment of two other molecules which are TNF receptor-associated factor 2 (TRAF2) and DD containing Receptor-interacting serine/threonine-Protein kinase 1(RIPK1) (Figure 1) (Ting *et al*., 1996; Hsu *et al*., 1996). Cellular inhibitors of apoptosis 1 and 2(c-IAP1 and c-IAP 2) present in a constitutive bound form to TRAF2 also get recruited along with TRAF2 and these c-IAP1/2proteins are E3 ligases which promote K11-,K63- and K48- linked ubiquitination of themselves and RIPK1 (Park *et al*., 2004). Modifications specific to K63- supports binding of transforming growth factor β-activated kinase 1 (TAK1) which is associated with TAK1 binding protein 2 and 3 (TAB2 and TAB3), IKK complex having NEMO (NF-□B essential modulator), IKK1/2 (IκB kinases 1 and 2) and linear ubiquitin chain assembly complex (LUBAC). LUBAC consists of three components which are E3 ligase HOIL-1 interacting protein (HOIP), haem-oxidised IRP2 ubiquitin ligase-1 (HOIL-1) and SHANK-Associated Rh Domain Interactor (Sharpin) which promotes linear ubiquitination of TNFR1, TRADD, RIPK1 and NEMO in TNFR1 Complex (Smit *et al*., 2012; Draber *et al*., 2015).

TNFR1 stimulation promotes cell survival by activating NF-κB which is present in association with its inhibitor (IκBα) in homodimeric form known as ReIA/p50 in unstimulated cells (Varfolomeev and Vucic, 2018).

NEMO which is present associated with IKK1 and IKK2 plays important role in activation of NFκB and is present in TNFR1 complex by interaction of its ubiquitin binding domain(UBD) to ubiquitin chains linked with M1-, K11- and K63- (Dynek *et al*., 2010). Kinase TAK1 phosphorylates and activates IKKs which in turn phosphorylates inhibitor of NF-κB (IκBα) and promotes ubiquitination by ubiquitin ligase complex SCF (Skp, Cullin, F box) which carries out polyubiquitination and proteasomal degradation of IκBα. Now NF-κb dimer (ReIA/p50) is translocated to nucleus and it initiates desired gene expression. TNFR1 signaling also works through activating MAP (Mitogen activated protein) kinase which includes RIP, p38, MKK 3/8 (Mitogen kinase kinase). In addition to promoting cell survival TNFR1 signalling also triggers programmed cell death (PCD) by induction of apoptosis which is achieved because of the presence of DD in TNFR1. Three type of TNFR1 related death receptors are present having DD in their ICD which are Fas and death receptor 4 and 5 (DR4 and DR5). Upon stimulation these death receptors recruit Fas-associated DD protein (FADD) which then consequently recruits caspase 8, caspase 10 and cellular FLICE- inhibitory protein (c-FLIP) to receptor through its Death Effector Domain (DED). Caspase 8 and 10 got self-activated by their oligomerisation which then leads to activation of downstream caspases 3 and 7 (Ashkenazi *et al*., 2014; Shalini *et al*., 2015; Tsuchiya *et al*., 2015).

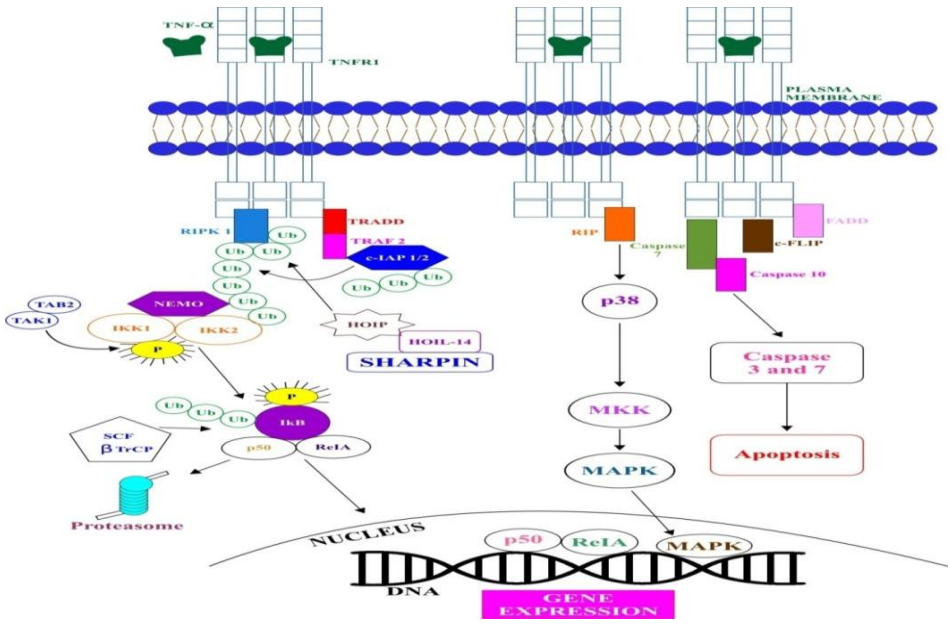

Figure 1: Signalling mechanism of TNFR1 (Varfolomeev and Vucic, 2018)

2.6.3.2 TNFR2 Signalling

TNFR2 signalling is largely involved in T cell survival and proliferation and it begins with recruitment of adaptor proteins TNF receptor associated factor (TRAF1 and TRAF2) which then recruit cIAP and carries signalling forward by binding to other adaptor proteins which are RIP, MKK3, p38 and NEMO/IKK. It ends with mobilization of activated transcription factor NF-κB or MAPK inside nucleus so that it can promote transcription of prosurvival genes. NF-κB is activated by degrading its inhibitor IκBα through ubiquitination and proteasomal degradation in SCF complex. Apoptosis by TNFR2 receptor involves recruitment of TRAF2, RIP, NEMO/IKK, NFκB and cFLIP protein in last which carries out apoptosis through caspases (Figure 2) (Faustman and Davis, 2010).

In previous time it was thought that TNFR2 signalling functions only for cell survival and proliferation but now it is proved that both TNFR1 and TNFR2 receptors are involved in mediating similar functions such as apoptosis, proliferation, cell differentiation and cytokine production and there is presence of functional overlap between two which depends on certain factors such as cell type, intracellular and extracellular cell environment, age, activation state of cell, NF-κB expression and cell injury. It is reported that a crosstalk occurs between both the receptors because of their coexistence on cell surface and under certain conditions TNFR2 activation can shift to TNFR1 apoptotic pathway and TNFR1 activation can shift to TNFR2 pathway (Fotin *et al*., 2002).

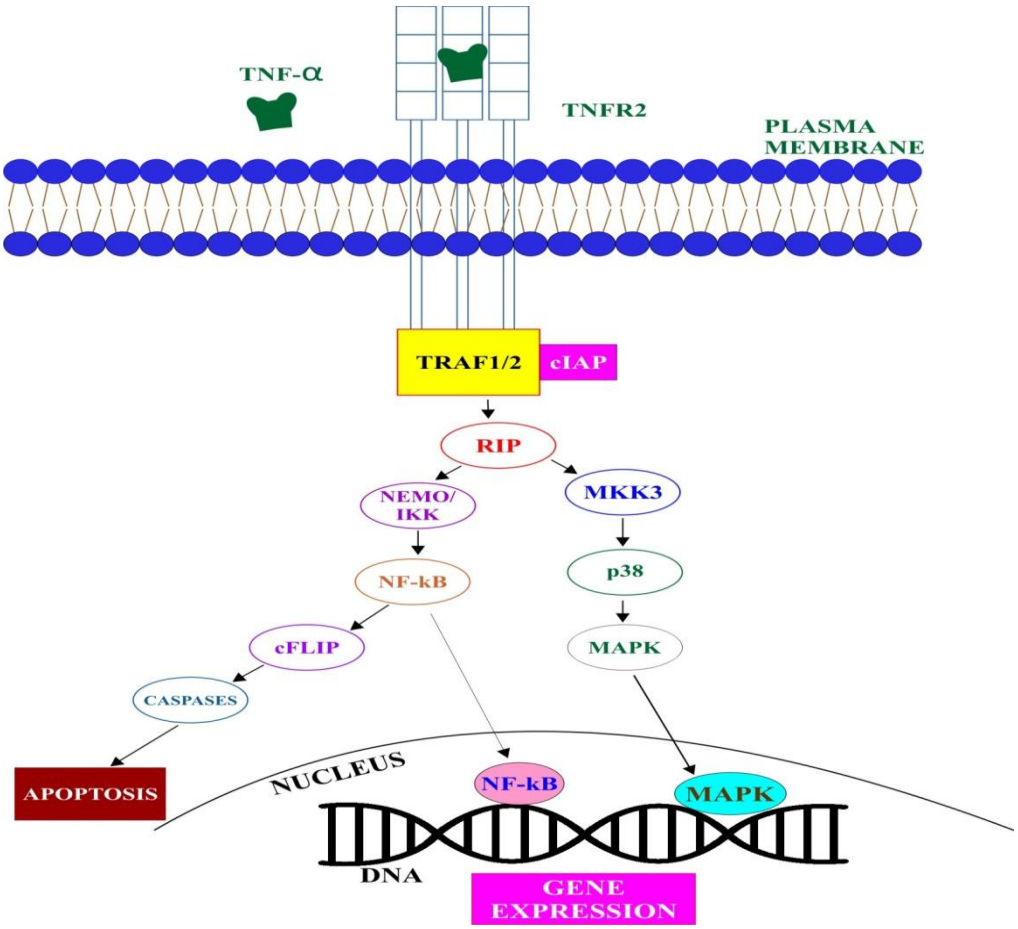

Figure 2: TNFR2 signalling pathway (Faustman and Davis, 2010)

7. Significance of TNF-α in TB:

Apoptosis of infected cells

TNF-α promotes direct killing and clearance of *M. tuberculosis* by carrying out apoptosis of infected cells and thus prevent it from spreading to other areas in vicinity (Figure 3) (Mootoo *et al*., 2009). However, this apoptotic role of TNF-α is counterbalanced by IL-10 which is an anti-inflammatory cytokine induced by *M. tuberculosis* components. Resistance against *M. tuberculosis* and outcome of infection is determined by balance between IL-10 and TNF-α (Rojas *et al*., 1999).

Promotes DC maturation and macrophage activation

Mature DCs and macrophages are formed from differentiation of myeloid cell precursors which is dependent upon presence of IL-4, GM-CSF and TNF-α (Santiagoschwarz *et al*., 1992). These DCs were able to induce resting CD4+ cells to secrete Th1 cytokines which are IL-2, IL-12, IFN-γ and IL-17. TNF-α acts over macrophages and activates them for their anti-*Mycobacerium* action by enhancing the production of ROI and RNI which are toxic to *M. tuberculosis* (Solisherruzo *et al*., 1988; Mootoo *et al*., 2009).

Role of TNF-α in production of chemokines and granuloma formation

Inflammatory chemokines produced by *M. tuberculosis* infected AMs and other lung epithelial cells govern cell

migration and localization which is needed for granuloma formation and TNF-α plays an important role in this process (Algood *et al*., 2003). Granuloma formation requires presence of certain chemokines such as CCL2, CCL5 and CCL8 which is induced by TNF-α by helping in early detection of chemokines and initiates recruitment of cells and helps in establishment of close associations between lymphocytes, neutrophils and macrophages (Roach *et al*., 2002). TNF-α absence leads to disorganized granuloma formation which further contributes to dissemination of *M. tuberculosis* infection (Algood *et al*., 2004).

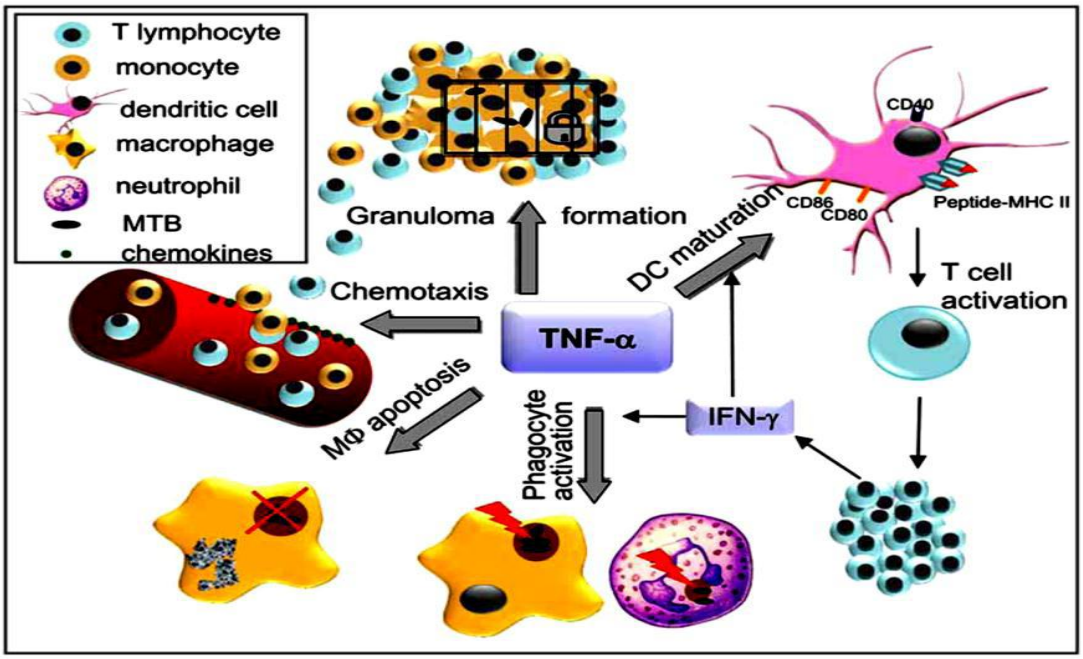

Figure 3: Role of TNF-α in immune system against TB infection (Mootoo et al., 2009)

8. Effect of TNF-α inhibitors

Rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythrematosus (SLE) are characterised by organ and tissue inflammation involving connective and supportive system of body which most commonly involves joints, but also sometimes tendons, ligaments, bones and muscles. RA which is a rheumatic autoimmune disorder involves attack of immune system via inflammatory cytokines over synovial tissue of joints leading to inflammation. TNF-α being a pro-inflammatory cytokine is involved in pathogenesis of rheumatic diseases and when released in excess it leads to severe inflammation and tissue damage. Due to this reason TNF-α inhibitors are used for treatment of immune mediated inflammatory rheumatic diseases such as RA, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease (Zuniga *et al*., 2012). TNF-α inhibitors involve chimeric human-murine monoclonal anti TNF-α antibody infliximab, human monoclonal antibody golimumab and adalimumab, and a TNF-α antagonist etanercept which is a soluble dimeric fusion protein that acts by binding to TNF-α receptor. Most common anti TNF-α agents approved by Food and Drug Administration (FDA) are etanercept and infliximab (Lyon and Rossman, 2017).

TNF-α inhibitors are reported to affect the activity of immune cells during *M. tuberculosis* infection as they block phagosome maturation, induce apoptosis of activated T cells and DCs and carry out complement dependent cytotoxicity (CDCC) of cytotoxic (CD8+) T cells which cause deleterious effect in development of effective immune response (Bruns *et al*., 2009; Zuniga *et al*., 2012). Blocking of TNF-α by TNF-α inhibitors cause breakdown of granuloma which results in dissemination of *M. tuberculosis* to other sites of body leading to EPTB and also reactivation of latent form of TB (Thalayasingam *et al*., 2011). When use of infliximab was approved by FDA in 1998 an increase in frequency of TB cases was reported in post-marketing surveillance and now it is recommended to check an individual for latent TB before exposing it to anti TNF-α therapy (Furst *et al*., 2007). Anti TNF-α drug consumption also enhance the risk for other bacterial infections such as *Salmonella*, *Legionella* and *Listeria* in addition to *M. tuberculosis* (Dixon *et al*., 2006).

9. Conclusion

TNF-α play a pivotal role in controlled maintenance of *M. tuberculosis* infection. It is reported through certain clinical studies that blocking of TNF-α by TNF-α inhibitors in patients with auto immune diseases lead to development of TB. But the mechanism of its action for protection against *M. tuberculosis* infection is complex and multivalent and is not clearly understood. Through this review we are aiming to gain some understanding about immunoregulatory actions of TNF-α which is of great significance and warrants further studies particularly in order of clinical implications that this field carries.

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