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The Role of N-Acetyl Cysteine in Pulmonary Tuberculosis

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ABSTRACT

Pulmonary tuberculosis is a chronic infection that is caused by Mycobacterium tuberculosis (MTB) infection and it is still the major health problem worldwide. MTB infection can induce oxidative stress. Some studies have proved that active TB patients have an association with excessive oxidative stress which causes glutathione (GSH) levels to decrease and free radicals to increase. GSH facilitates the control of MTB intracellular bacterial growth in macrophages and has direct antimicrobial activity. N-acetyl cysteine (NAC) is a thiol, a precursor of L-cysteine and GSH that has been used for decades as a mucolytic agent in the treatment of respiratory diseases. Some studies have reported a beneficial role of NAC as an immunomodulator, besides, it also has anti-inflammatory and antimicrobial effect in TB management.

Keywords: *immunotherapy, NSCLC, immune checkpoint inhibition*

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INTRODUCTION

Pulmonary tuberculosis is an infectious disease caused by Mycobacterium tuberculosis (MTB). Tuberculosis (TB) is one of the major public health global problems. 10 million people infected by TB and 1.6 million died of the disease according to World Health Organization (WHO) report in 2017.[1] Based on the number of TB incidents, Indonesia ranked in number three with 845,000 (770,000 – 923,000) incidents.[2]

Tuberculosis management is very complex, it requires a minimum of 6 months of treatment with a risk of drug toxicity. Along with drug resistance in tuberculosis patients, tuberculosis management is currently being developed. WHO develops immunotherapy and adjunctive therapy to enhance immunity in TB patients.[3] Lung cancer is the leading cause of death in developed countries in the world. In 2017, American Cancer Society found 222,500 lung cancer cases, 116,990 of whom were men and 105,510 women.[1-3]

The human body has a defense system consisting of innate immune system and adaptive immune system against MTB. In TB patients, there is an increase in proinflammatory cytokines, namely IL-1, IL-6, and TNF-α. Active TB has an association with suppression of T cell responses and increased production of immunosuppressed cytokines, namely IL-10 which can inhibit T cell proliferation and IFN- γ production.[4]

MTB infection can induce oxidative stress.[5] Oxidative stress results from an imbalance between reactive oxygen species (ROS) and antioxidants. Cells have several endogenous antioxidants as defense mechanisms, they are vitamin C, vitamin E and SOD enzymes, catalase, glutathione peroxidase, and endogenous thiol.[6]

N-acetyl cysteine (NAC) is a thiol, a precursor of L-cysteine and glutathione (GSH) that has been used for decades as a mucolytic agent in the treatment of respiratory diseases. NAC in tuberculosis is used as a mucolytic, antioxidant, anti-inflammatory, protective and hepatoprotector.[6, 7]

In this literature review, we will discuss NAC as immunomodulators in tuberculosis.

Lung Tuberculosis

Definition of Tuberculosis

Tuberculosis (TB) is a disease caused by the infection of the microorganism MTB. Pulmonary tuberculosis is tuberculosis which attacks the lung tissue. Transmission generally occurs from an infected person to another person via droplets or with coughing up blood or contaminated sputum.[1, 8]

Tuberculosis Epidemiology

About one-third of the world's population is infected with TB germs, but only 5-10% develop into

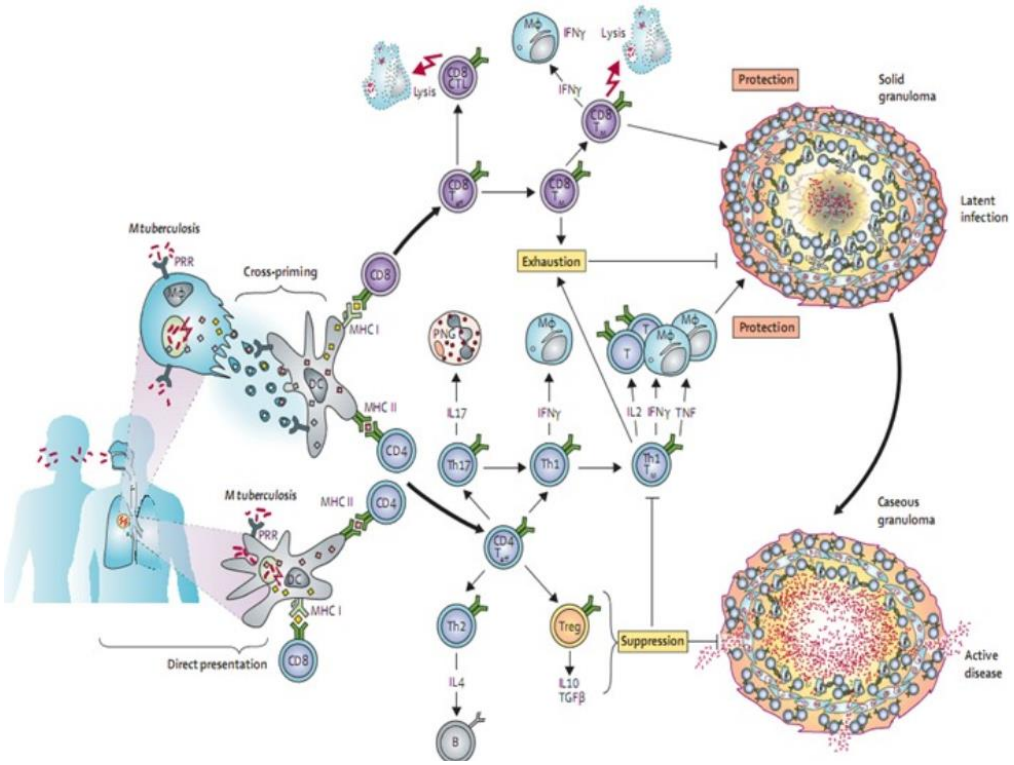

Figure 1. Immune response against *Mycobacterium tuberculosis*

disease. The World Health Organization (WHO) report in 2015 stated that there were 10.8 million new cases of tuberculosis with estimated mortality from tuberculosis reaching 1.8 million. In Indonesia, based on the 2001 Survei Kesehatan Rumah Tangga (SKRT), it was found that diseases of the respiratory system were the second leading cause of death after the circulatory system3,8 The largest number of deaths due to TB is in Southeast Asia, which is 625,000 people or a mortality rate of 39 people per 100,000 population.[1, 8]

Immunity to Tuberculosis

The human body has a defense system consisting of the innate immune system and the adaptive immune system against pathogenic microorganisms. Immunity to MTB initiated by the innate immune system is mediated by neutrophils, macrophages, NK cells, and T γδ cells, while the adaptive immune system is mediated by T lymphocytes cells and B cells, as shown in Figure 1.

Tuberculosis bacilli that enter through the airways will nest in the lung tissue, microorganism molecules called PAMP (Pathogen-associated molecular patterns) will be identified through a special pathway called pattern recognition receptor (PRR) and activate the immune system. The natural immune system is the initial defense against TB, if it fails then TB bacilli will spread through macrophages to lymph nodes and blood flow to many organs.[4, 9]

The initial response to the tissue that has never been infected is in the form of an inflammatory cell, both polymorphonuclear neutrophils (PMN) cells and

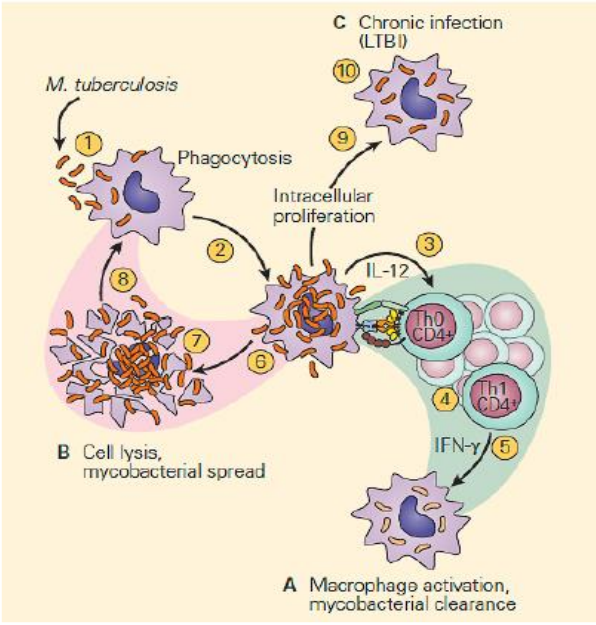

Figure 2. Scheme of the interaction between macrophages and *Mycobacterium tuberculosis*[10]

phagocyte cells mononuclear. Bacilli that enter alveoli will be ingested and destroyed by alveolar macrophages. The interaction between macrophages and MTB as represented in Figure 2 can occur in 3 forms. First, macrophages can successfully kill MTB. Second, bacilli proliferate in cells and eventually kill phagocytic cells. Third, MTB microorganisms will be able to live in macrophages, both of them survive and cause a chronic infection. Meanwhile, mononuclear cells multiply and

form aggregates. MTB proliferate continuously, and while macrophages (which contain bacilli) die, mononuclear cells enter the tissue and ingest newly released MTB.[10]

Activated macrophages can kill or inhibit the bacilli. Macrophages can also act like an APC (antigen-presenting cell) where MTB in macrophages will be presented to CD4 T lymphocyte cells through a major histocompatibility complex (MHC) class II. Th1 cells then secrete IFNγ which activates macrophages so that they can destroy bacilli that have been phagocyted. If the bacilli remain alive and release their antigens to the cytoplasm, it will stimulate CD8 T cells through MHC class I. Cytolytic CD8 cells will then lyse macrophages.[11]

The adaptive immune system played by T cells is the main mediator of immune defense against Mycobacterium tuberculosis. T cells consist of T helper lymphocytes, also called CD4+, accounting for 65% of peripheral blood T lymphocytes. Another small portion (35%) is cytotoxic T lymphocytes and is often called CD8. T Helper cells (CD4) proimageliferate and differentiate into T helper 1 (Th1) cells and T helper 2 (Th2) cells. T cell subsets cannot be morphologically differentiated but can be distinguished from the different cytokines that they produce. Th1 cells produce type 1 cytokines, including IL-2, IL-12, IFN-γ, and tumor necrosis factor-alpha (TNF-α).[4, 12] Cytokines released by Th1 are effective activators to generate cellular immune responses. Th2 cells make and release type 2 cytokines including IL-4, IL-5, IL-6, IL-9, and IL-10. Type 2 cytokines inhibit Th1 cell proliferation, whereas type 1 cytokines inhibit the production and the release of type 2 cytokines.[12-14]

Cytotoxic cells can directly or indirectly kill inactivated macrophages that contain MTB that are actively dividing in their cytoplasm. Cytotoxic T cells will secrete their granulasyn, granzym, and perforin to kill the cells infected with MTB. The death of inactivated macrophages will eliminate the intracellular environment (a good place to grow), replaced with an extracellular environment in the form of solid tissue (necrotic) that will inhibit the growth of MTB.[13, 14]

In TB patients, there is an increase in proinflammatory cytokines, namely IL-6, TNF-α, and IL-1. Increased proinflammatory cytokines can cause fever, cachexia, and necrosis. Active TB has an association with suppression of T cell responses and increased production of immunosuppressed cytokines, namely IL-10 which can inhibit T cell proliferation and IFN-γ production.[9]

In some hosts, the ability to enhance immune response is weak, so that it is unable to control the growth of MTB. The host will clinically suffer from TB a few weeks to months after primary infection. Included in this group are infants, elderly, and immunocompromised.

Oxidative Stress in Tuberculosis

Oxidative stress

Oxidative stress occurs due to an imbalance between reactive oxygen species (ROS) and antioxidants. Under normal circumstances, the amount of endogenous ROS is regulated in the required level. ROS is produced by mitochondria in cells through normal metabolism, the conversion of oxygen (O_2) to water (H_2O). Include in it are radical superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH). ROS and RNS in low concentrations are needed physiologically, for example as a defense against infectious agents. Excessive amount of ROS causes an imbalance between oxidants and antioxidants.[6, 7]

ROS can modify and destroy macromolecules in cells, including oxidation and peroxidation of DNA. Proinflammatory cytokines and growth factors stimulate the production of ROS as a signaling mediator. Inhaled air consisting of ozone, nitrogen dioxide, diesel exhaust, and cigarette smoke can cause oxidative stress.[6]

Oxidative stress occurs because of responses to the production of ROS and RNS during the process of metabolic reactions. Oxidative stress due to an imbalance between ROS and antioxidants can cause tissue damage, inactivation of anti-proteases, mucous hyper-secretion, bronchial wall edema, bronchoconstriction, and increase inflammation through activation of redox-sensitive transcription factors in leukocytes.[6]

Physiologically, cells have several endogenous antioxidants as defense mechanisms against free radicals, namely vitamin C, vitamin E and Superoxide dismutase (SOD) enzymes, catalase, glutathione peroxidase, and endogenous thiol.[7]

Glutathione (GSH), a tripeptide antioxidant, plays an important role in cellular homeostasis. GSH plays a vital role in maintaining cellular redox conditions, it takes peroxides that can harm cells. GSH also plays a role in normal immune system by increasing lymphocyte activity. A decrease in GSH levels has an association with CD4 T cell lymphocyte apoptosis.[15]

Oxidative stress in TB

MTB infection can induce oxidative stress. Previous studies have suggested that active TB patients have an association with excessive oxidative stress with a decrease in antioxidant concentration and increased free radicals.[5, 9]

The oxidative environment normally helps to kill pathogenic microorganisms. However, in the intracellular pathogen of MTB, the opposite can grow well in macrophages in environments with high oxygen concentrations. This is also demonstrated through tuberculous lesions that are often found in tissues with high PaO_2, for example in the lung apex area.[16]

In cells infected with MTB, oxidative stress comes from both endogenous and exogenous sources (Figure 3). Endogenous sources are aerobic respiration products and ETC (*electron transport chain*) where O_2 is used as a terminal electron receiver. Exogenous factors that trigger oxidative stress on MTB can be either cigarette smoke or air pollution.

Inflammation in TB triggers oxidative stress and results in low levels of glutathione in TB patients caused by reactive oxygen intermediates (ROI) and TNFα.[9]

GSH facilitates the control of MTB intracellular bacterial growth in macrophages and has direct anti-

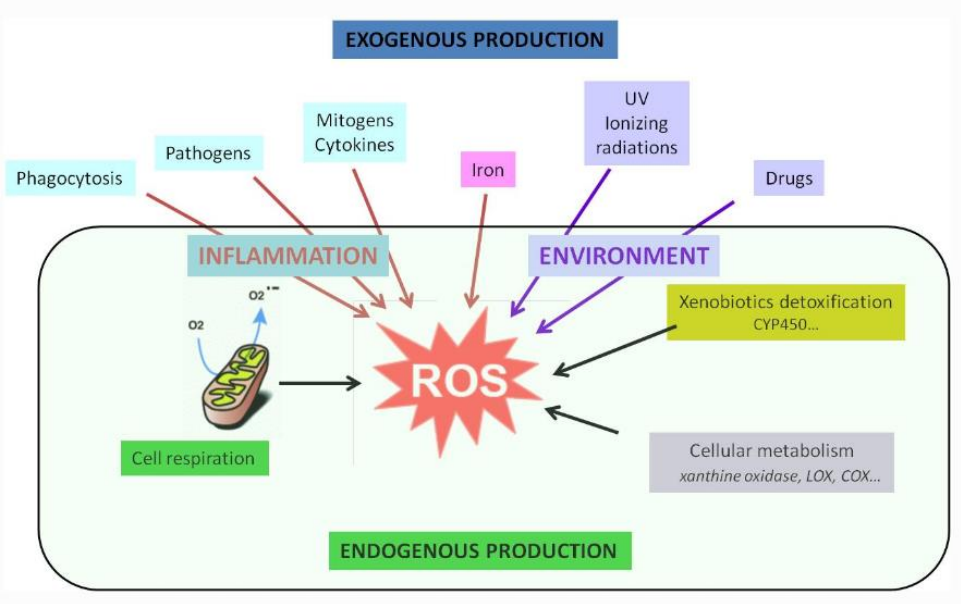

Figure 3. Endogenous and exogenous factors trigger ROS formation

microbial activity. The rate of synthesis of GSH is limited by cysteine and the γ-glutamylcysteine synthetase (γ-GCS) enzyme. Cysteine is an essential amino acid in humans which levels are limited. Low plasma cysteine concentration is 10-25 µmol/L. Cysteine is immediately oxidized to extracellular cystine and once cystine is in the cell it will immediately reduced to cysteine which is used in the synthesis of GSH.[15]

T helper 1/T helper 2 (Th1/Th2) balance theory is important in immune response to MTB. The polarization of CD4+ naive T cells (Th0) to Th1 or Th2 is determined by the produced cytokines. Th1 cytokines are important for controlling intracellular pathogens, including MTB. Polarization of CD4+ naive T cells will easily lead to Th2 predominance through depletion of intracellular GSH levels and vice versa. If intracellular GSH levels increase, it will be more dominant towards Th1.[12]

N-acetyl cysteine (NAC)

N-acetyl cysteine (NAC) is thiol, a precursor of L-cysteine and GSH that has been used for decades as a mucolytic agent in the treatment of respiratory diseases.[7]

Pharmacology and pharmacokinetics of NAC

NAC has chemical formula of $C_5H_9O_3S$ and molecular weight of 163.2. NAC can be given per inhalation, intravenously, or per oral. NAC is well orally absorbed at a dose of 600 mg. The half-life of plasma is 2.5 hours and no NAC is detected after 10-12 hours. Increasing the dose of NAC also increases the bioavailability of NAC. Higher concentrations of NAC can be obtained through intravenous administration.[7]

Oral administration of NAC is metabolized mainly in intestinal cells and liver cells, are absorbed rapidly, and combined with protein peptide chains to form active metabolites of NAC (cysteine and reduced GSH). The formed cysteine limits the synthesis of GSH by the enzyme γ-glutamylcysteine synthetase (γ-GCS) or glutamate cysteine ligase (GCL). The redox pair of extracellular cysteine in the extracellular plasma compartment provides an independent ambient redox environment for immune cell circulation. The redox status of extracellular cysteine arises as a new mechanism of signal transduction that can induce changes in post-translation in a redox down state. Changes in post-translation include producing dynamic modulation of the functions and activities of various enzymes, transcription factors, receptors, adhesion molecules, and membrane protein signals.[17]

NAC is generally safe. Oral administration of 600 mg/day or less can be well tolerated without side effects. NAC doses of 1800 mg/day were also reported without side effects and did not affect the outcome. Minor side effects such as erythema, sweating, and gastrointestinal reactions including dyspepsia and diarrhea happen when NAC is given 150 mg/kg orally. The most common side effects associated with high doses of NAC are reported complaints of nausea, vomiting, and other gastro-intestinal disorders.[7]

Therapeutic effects of NAC

NAC has the benefit of reducing lung inflammation, transplant rejection, and pulmonary fibrosis. NAC protects the lungs from histopathological changes due to exposure of free radicals, bronchial inflammation, emphysema, and precancerous lesions. NAC can inhibit TGF-β signaling which can cause pulmonary fibrosis and inhibit the growth of endothelial cells in the arteries. NAC can be absorbed quickly at a dose of 600mg.

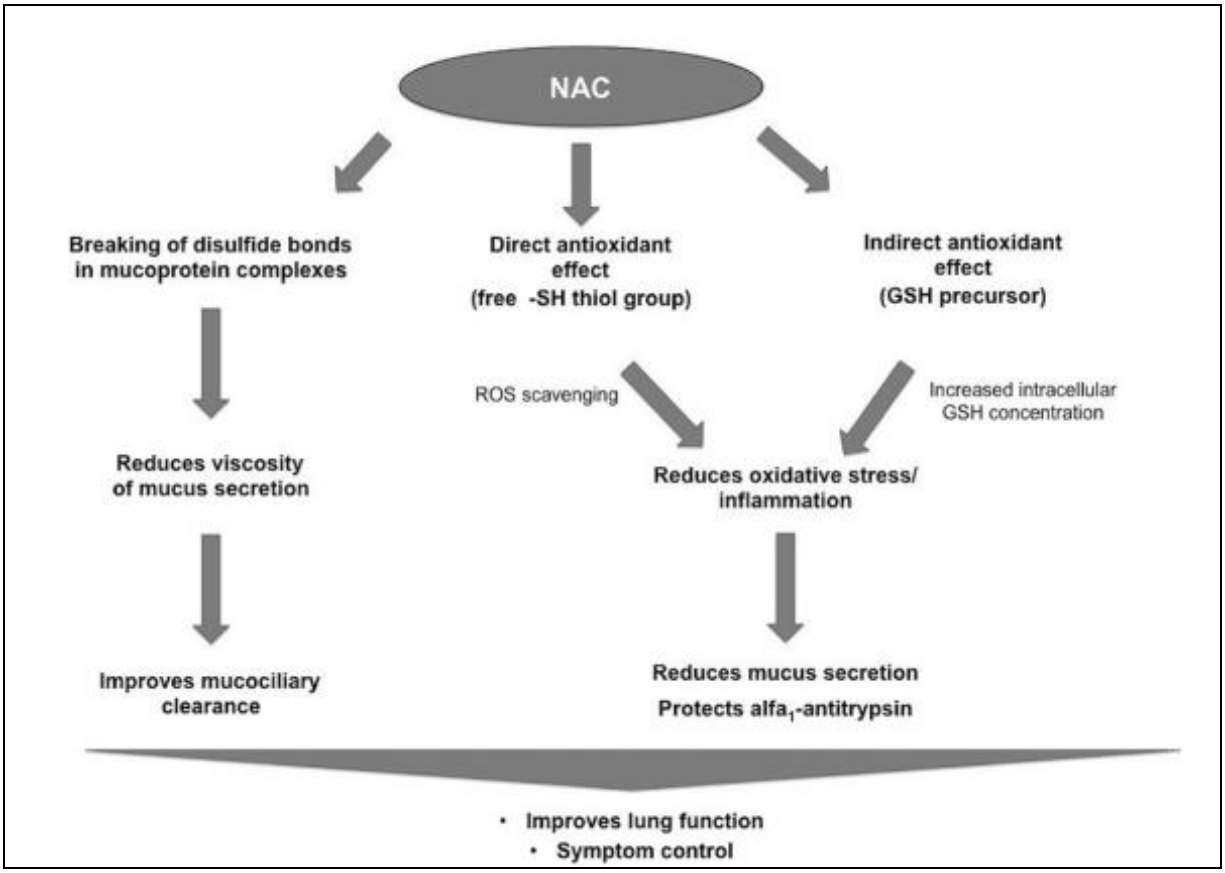

Figure 4. The role of NAC in respiratory system[6]

The role of NAC as in **Figure 4** is as an antioxidant, anti-inflammatory, and immunomodulator.

a. NAC as an Antioxidant

NAC can stimulate GSH, plays a role in detoxification as well as antioxidants. NAC given 600 mg orally does not change the levels of cysteine and glutathione on Bronchoalveolar lavage fluid (BALF) in healthy people. A higher dose of NAC is needed to increase GSH levels. In conditions with oxidative stress, doses of more than 600 mg are needed to change the levels of gluthatione.[7]

NAC can also reduce free radicals such as OH, H_2O_2, and O_2. NAC reacts with O_2 and NO. The constant rate of NAC reaction with O_2^-, H_2O_2, and peroxynitrite is relatively low. Instead, NAC reacts with free radicals such as OH, NO_2 and CO_3^- and is able to bind redox-active metal ions.[17]

b. NAC as an Anti-inflammatory

Inflammatory response is strongly influenced by the redox sensitive factor nuclear kappa β transcript (NF-κβ) which regulates some of proinflammatory genes and mediates immune response. Some in vitro studies show that the decrease in inflammatory mediators has a correlation with NF-κβ inhibitory activity.[7]

NAC can affect the expression of thioreduxin and glutaredoxin. Thioreduxin increases DNA binding to NF-κβ by reducing cysteine, whereas glutaredoxin through changes in the redox status of GSH is involved in changes of signal transduction which results in a biological response. NAC decreases the release of thioreduxin and glutaredoxin and weakens the binding of DNA by NF-κβ, which causes a disruption in inflammatory response.[7]

NAC can inhibit the activation of c-Jun N-terminal kinase, p38 MAP kinase, and redox-sensitive activating protein-1 and nuclear factor kappa B transcripts (NF-κβ). NAC can also prevent apoptosis and increase cell survival by activating kinase regulating extracellular pathway signals.[7]

David and Nelson suggested that NAC can inhibit the production of proinflammatory cytokines in the lungs infected with pathogenic microorganisms. Continuous high dose of 100 mg/kg IV NAC per day can effectively reduce CRP and oxygen requirements, as well as improve clinical output in severe pneumonia and septic shock associated with H1N1 virus.[18]

NAC as Immunomodulator

Immunomodulators are drugs that are used to help regulate or normalize the immune system. For example, immunomodulators that are used as adjunctive therapies to treat asthma and others.[19]

Benefits of immunomodulators in general, namely to prevent infection, prevent secondary infection, control infection, and obtain the results of an

early clinical response. While the main purpose of immunomodulators and immunotherapy in TB is to increase the potential of the host immune system so that it can be better to control TB, it also strengthen natural immunity against the risk of opportunistic infections and fight the biological effects on hosts by inducing the production of beneficial cytokines, inhibiting the production of dangerous proinflammatory cytokines, and stimulates immune cell activity in general.[20]

NAC can act as an immunomodulator, clinically NAC can improve symptoms of Sjogren's syndrome, improve T-cell effector function, and delay the decline in CD4 levels in HIV patients. Administration of NAC in menopausal women increases phagocytic function, leukocyte chemotaxis, NK cell function, and a decrease in TNF-α and interleukin-8.[17]

NAC influences cellular and humoral immunity by inhibiting the production of poloclonal immunoglobulins from B lymphocyte cells by reducing the expression of B-cell co-stimulatory surface molecules (CD40 and CD27) and IL-4 production.[17]

NAC in Tuberculosis

a. NAC as an Antioxidant

Inflammation in TB triggers oxidative stress and results in low levels of gluthatione in TB patients, caused by ROI and TNFα. NAC can stimulate GSH, plays a role in detoxification, and as an antioxidant.[7]

b. NAC as an Anti-inflammatory

In TB patients, there is an increase in proinflammatory cytokines, namely IL-6, TNF-α and IL-1. Increased proinflammatory cytokines can cause fever, cachexia, and necrosis. Active TB has an association with suppression of T cell responses and increased production of immunosuppressed cytokines, namely IL-10 which can inhibit T cell proliferation and IFN-γ production.[9]

NAC can inhibit the production of proinflammatory cytokines in the lungs infected with pathogenic microorganisms.[18]

c. NAC as an Antimicrobial

Some studies report NAC in high concentrations can inhibit the growth of some bacteria. The antibacterial mechanism of NAC is thought to prevent the use of amino acid cysteine in bacteria or the reaction of sulfhydryl groups on NAC with proteins in bacterial cells.[21]

NAC has a microbicidal effect and can inhibit the infection of the microorganism MTB by suppressing the host's oxidative response. NAC inhibits oxidative stress, lipid peroxidation, DNA oxidation, and cell death in macrophages infected with MTB.[22]

d. NAC as an Immunomodulator on TB

Low intracellular GSH levels can reduce the cytotoxic function of NK cells. GSH can inhibit MTB intracellular growth through bacteriostatic mechanisms. GSH can increase cytolytic activity in NK cells through demonstration of cytotoxicity measurements. NK cells need FasL and CD40L to inhibit MTB growth. The administration of GSH can increase NK cell activity through promoting interaction between Fas and fas Ligand and CD40 and CD40L, as shown in **Figure 5**. NAC therapy can increase intracellular levels of GSH.[23, 24]

Devin Morris, *et al*. mentioned in their research that NAC therapy can increase GSH levels and reduce intracellular MTB growth by increasing the function of the natural immune system by increasing macrophage activity. GSH can also control MTB by increasing the activity of T lymphocytes and NK cells.[25] NAC therapy can increase intracellular levels of GSH. Some clinical studies report NAC supplementation can increase gluthathione levels by giving a dose of 600-1800mg per day.[26]

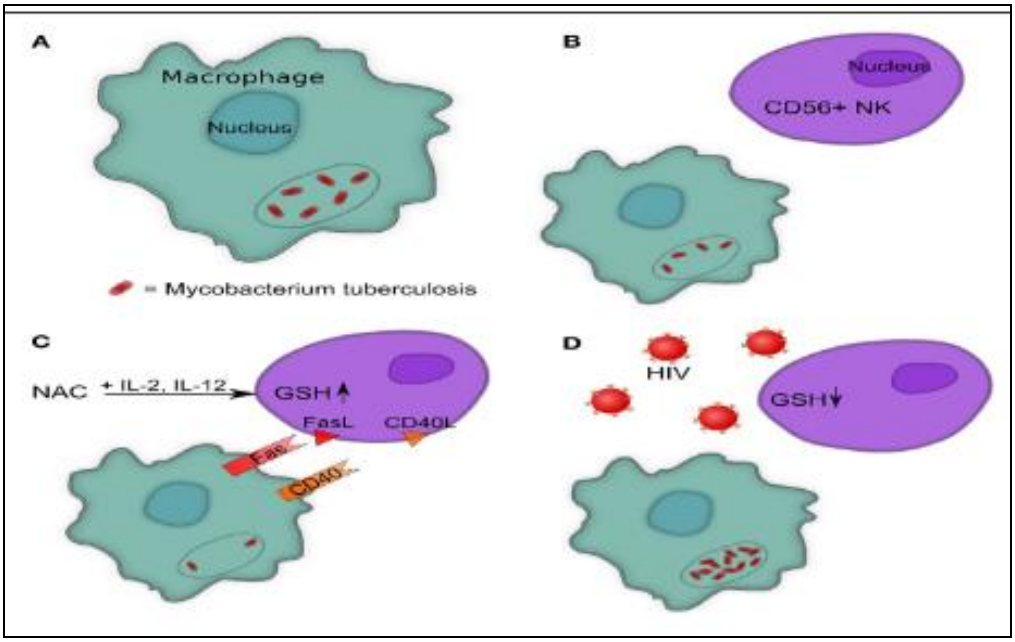

Figure 5. GSH increases NK cells cytolytic effectivity[23]

Research by Vishwanath and colleagues suggests that NAC can control intracellular immunity more efficiently. NAC can also reduce the levels of proinflammatory cytokines, such as IL-6, TNFα, and IL-1 in TB patients.[4] NAC and several other antioxidants have the ability to reduce IL-1β production by limiting inflamasom activation. Inflamasom together with the NLRP3 protein act as obligates in the formation of IL-1β, both of which activate caspase-1, which can convert pro-IL-1β proteins to IL-1β maturing.[27]

NAC influences cellular and humoral immunity by inhibiting the production of poloclonal immunoglobulins from B lymphocyte cells by reducing the expression of B-cell co-stimulatory surface molecules (CD40 and CD27) and IL-4 production.[17]

Research by Guerra, *et al.* mentions that *in vitro* blood cultures of HIV patients infected with H37Rv produce levels of proinflammatory cytokines IL-1, TNF-α, IL-6 higher than healthy controls. Therapy with NAC 10 mM increases IFN-γ, IL-12, IL-2 levels and decreases IL-1, TNF-α, and IL-6 levels. This finding shows the beneficial role of NAC in the treatment of TB.[15]

Khameneh and colleagues in their study compared the effectiveness of a combination of OAT therapy with NAC. From 96 patients, it was found that NAC was less effective in increasing the effectiveness of OAT.[8] The effectiveness of NAC as an immunomodulator on TB still shows variable results, so further research is needed to establish the beneficial effects of NAC with co-administration of OAT.

SUMMARY

Tuberculosis (TB) is an infectious disease with a high mortality rate. High resistance, failure of BCG vaccine, high incidence of AIDS, and TB treatment resistance contribute to the failure of TB treatment. Tuberculosis management is currently being developed and new drugs are needed. N-acetyl cysteine (NAC) in tuberculosis has therapeutic effects, such as mucolytic, antioxidant, anti-inflammatory, and hepatoprotector to prevent the occurrence of DIH, or as an immunomodulator. NAC can act as an immunomodulator, increase the effector function of T cells, delay the decrease in CD4 levels, improve phagocytic function, leukocyte chemotaxis, NK cell function, and decrease TNF-α and interleukin-8. The effectiveness of NAC as an immunomodulator on TB still needs further research.

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