

Tumor Necrosis Factor Alpha

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Introduction

Tumor Necrosis Factor Alpha (TNF α) is a type of cell signalling protein or cytokine with a molecular weight of 25 kDa. Also known as cachectin or cachexin, it plays an important role in inflammation. It exists in two forms: a soluble trimeric form or a membrane-bound form. It was first reported by Dr. Gale A. Granger in 1968, who observed the lymphocytes producing a cytotoxic factor. He called the factor lymphotoxin or LT. At almost the same time, Dr. Nancy H. Ruddle reported the same phenomenon, and hence, the discovery is credited to both Dr. Ruddle and Granger. However, the name "tumour necrosis factor" was suggested by Dr Loyd J. Old in 1975 when he reported that macrophages produce another factor. The first TNF was successfully cloned in 1984. Further research led to LT being renamed as TNF β and TNF as TNF α .

Production

Initially, macrophages were considered to be the primary producers of TNF. However, with time, it was discovered that numerous other types of cells also produce it. These types of cells include mast, lymphoid, NK and endothelial cells, neurons, adipose tissue, neurons, cardiac myocytes, eosinophils, neutrophils and CD4+ lymphocytes.

Major Roles of TNF α

Tumor necrosis factor alpha (TNF α) is produced in the body mainly by macrophages and impacts the physiological processes of the human body in a vast number of ways. It regulates the immune system of the body and acts as a mediator in the immune response. It performs these functions by activating the eosinophils and the neutrophils. Furthermore, it also has a profound impact on the vascular endothelium. It has also been demonstrated to enhance antiviral activity, resulting in fluctuations in the metabolism of lipids. As a regulator, excessive amounts of TNF α produced during diseases worsen the health of the individuals suffering from the illness. (Aggarwal, 2003) It has also been found to play the role of mediation of inflammatory diseases of the joints, rejection of the allograft, a few parasitic forms of infections, endotoxic shocks and cachexia related to various types of malignant diseases.

TNF α plays an important role in the physiology of human beings, especially the regulation of the immune cell. As it is a pyrogen, it may result in inflammation or apoptotic cell death. Moreover, it inhibits viral replication and tumorigenesis. Therefore, its regulation is vital for the proper functioning of the human body. Any fluctuations in its levels may lead to various diseases like cancer,

inflammatory bowel disease, Alzheimer's, psoriasis and major depression. $\text{TNF}\alpha$ stimulates the hypothalamus and liver. It also stimulates phagocytosis and several other tissues. The cytokine enhances the resistance to insulin and plays a vital role in the regulation of the perception of bitter taste.

Reception and Signaling

Two receptors, namely TNFR1 and TNFR2, can bind $\text{TNF}\alpha$. The receptor TNFR1 has a molecular weight of 55 kDa, and TNFR2 has a weight of 75 kDa. Both these receptors belong to the superfamily of tumour necrosis factor receptors or TNFRSF. The receptor TNFR1 can bind both forms of $\text{TNF}\alpha$, soluble and the one bounded by a membrane. This receptor is expressed in a wide variety of tissues. On the other hand, TNFR2 generally exists in the cells found in the immune system of the body and can merely bind the form of $\text{TNF}\alpha$ bound by a membrane. Hence, the role played by TNFR2 is often underestimated, as TNFR1 is the main source of information related to the signalling of $\text{TNF}\alpha$.

The cytokine activates the following three pathways.

- The nuclear factor kappa light chain enhancer of activated B cells (NF- κ B)
- The mitogen-activated protein kinase (MAPK)
- And the death signalling.

Therapeutic Applications

$\text{TNF}\alpha$ acts towards the promotion of inflammation and, hence, is a cause of a variety of autoimmune diseases. These disorders may include inflammatory bowel disease (IBD), asthma, psoriasis, ankylosing spondylitis, [rheumatoid arthritis](#) and hidradenitis suppurativa. Therefore, in some instances, these types of diseases may be treated through the utilization of TNF inhibitors. (Bradley, 2008) The treatment works by directly binding the inhibitor, such as a monoclonal antibody (like infliximab), to $\text{TNF}\alpha$. These antibodies form a much stronger bond with $\text{TNF}\alpha$ as compared to the TNFR receptors.

However, thus far, the cytokine has limited clinical and therapeutic applications and is currently limited to the treatment of patients suffering from cancer in phase 1 and 2 trials. Still, the exact efficacy of the treatment is not yet proven. There has been a lot of research regarding the potential therapeutic applications of the cytokine to treat cancer in combination therapy. The research conducted by various scientists suggests the possibility of $\text{TNF}\alpha$ being able to interact with other cytotoxic drugs and biological agents. Moreover, the medical community is discussing the potential of utilizing particular antibodies to function as inhibitors to $\text{TNF}\alpha$ production and counteract neoplastic disease and septic shock.

Furthermore, in the context of anti-TNF therapy, the treatment of infliximab has proven to be

somewhat effective in the prolonged stabilization of renal cell carcinoma. Further tests have been conducted on patients suffering from ovarian and breast cancers by the utilization of etanercept, and some patients have shown signs of prolonged stabilization of the disease.

References

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Bradley, J. R. (2008). TNF-mediated inflammatory disease. *Journal of Pathology*, 214(2), 149–160. <https://doi.org/10.1002/path.2287>