TNFAIP3

A20 protein, also known as TNFAIP3

(tumor necrosis factor alpha-induced protein 3), is a multifunctional protein that plays a critical role in regulating the immune response and preventing inflammation. A20 was first identified as a gene that is rapidly induced in response to tumor necrosis factor-alpha (TNF-alpha), a proinflammatory cytokine that is involved in a wide range of immune and inflammatory responses.

A20 is primarily expressed in immune cells, including B cells, T cells, dendritic cells, and macrophages, where it acts as a negative regulator of the NF-kB signaling pathway, which is a key pathway that regulates the expression of proinflammatory cytokines and chemokines. A20 functions as a deubiquitinase, removing ubiquitin chains from key signaling molecules, such as TRAF6, which is an important adapter protein in the NF-kB pathway. By deubiquitinating TRAF6 and other signaling molecules, A20 helps to limit the amplitude and duration of NF-kB signaling, thereby preventing excessive inflammation.

In addition to its role in regulating the NF-kB pathway, A20 has also been shown to play a role in regulating other signaling pathways involved in the immune response, including the JNK, p38 MAPK, and IRF3 pathways. A20 has been implicated in a wide range of immune-mediated diseases, including autoimmune disorders, infectious diseases, and cancer. Mutations in the A20 gene have been associated with various autoimmune disorders, including systemic lupus erythematosus (SLE), rheumatoid arthritis, and inflammatory bowel disease (IBD).

Studies have shown that A20 can be induced by various stimuli, including inflammatory cytokines, toll-like receptor (TLR) ligands, and microbial products. Thus, A20 is thought to play a critical role in maintaining immune homeostasis and preventing excessive inflammation in response to various environmental stimuli.

It's mechanism of action in the regulation of ferroptosis and inflammation after stroke is still unknown.

In a study, the A20-knockdown BV2 cell line (sh-A20 BV2) was constructed at first, and the oxygen-glucose deprivation/re-oxygenation (OGD/R) cell model was constructed. Both the BV2 and sh-A20 BV2 cells were treated with the ferroptosis inducer erastin for 48 h, and the ferroptosis-related indicators were detected by western blot. The mechanism of ferroptosis was explored by western blot and immunofluorescence. Under OGD/R pressure, the oxidative stress level of sh-A20 BV2 cells was inhibited, but the secretion of the inflammatory factors TNF-α, IL-1β, and IL-6 was significantly upregulated. And sh-A20 BV2 cells had higher expression levels of GPX4 and NLRP3 proteins under OGD/R induction. Western blot further confirmed that sh-A20 BV2 cells inhibited OGD/R-induced ferroptosis. Under the effect of erastin of the ferroptosis inducer (0-1000 nM), sh-A20 BV2 cells had higher cell viability than wild-type BV2 cells and significantly inhibited the accumulation of ROS and the level of oxidative stress damage. It was confirmed that A20 could promote the activation of the IκBα/NFκB/iNOS pathway. It was confirmed by an iNOS inhibitor that iNOS inhibition could reverse the resistance effect of BV2 cells to OGD/R-induced ferroptosis after A20 knockdown. In conclusion, this study demonstrated that inhibition of A20 mediates a stronger inflammatory response while enhancing microglial resistance by knocking down A20 in BV2 cells [1)].

It is overexpressed both in human glioma tissues and cell lines and inhibiting A20 expression greatly slowed tumor cell growth in culture and in mice. These findings indicated that A20 is involved in the tumorigenesis of human glioma, and may serve as a future therapeutic target [2)]

Results offer strong evidence for TNFAIP3 as a key regulator of the cytoplasmic signaling to activate NF-kappaB en route to O6-alkylating agent resistance in glioblastoma cells. This pathway may be an attractive target for the therapeutic modulation of glioblastomas [3)].

1)
Liu X, Jin X, Wang X, Yan X, Wang C, Wang K, He X, Zhai W. Knockdown of A20 attenuates microglial susceptibility to OGD/R-induced ferroptosis and upregulates inflammatory responses. Immunopharmacol Immunotoxicol. 2023 Mar 9:1-13. doi: 10.1080/08923973.2023.2189061. Epub ahead of print. PMID: 36891829.
2)
Guo Q, Dong H, Liu X, Wang C, Liu N, Zhang J, Li B, Cao W, Ding T, Yang Z, Zhang X. A20 is overexpressed in glioma cells and may serve as a potential therapeutic target. Expert Opin Ther Targets. 2009 Jul;13(7):733-41. doi: 10.1517/14728220903045018. PMID: 19492975.
3)
Bredel M, Bredel C, Juric D, Duran GE, Yu RX, Harsh GR, Vogel H, Recht LD, Scheck AC, Sikic BI. Tumor necrosis factor-alpha-induced protein 3 as a putative regulator of nuclear factor-kappaB-mediated resistance to O6-alkylating agents in human glioblastomas. J Clin Oncol. 2006 Jan 10;24(2):274-87. doi: 10.1200/JCO.2005.02.9405. Epub 2005 Dec 19. PMID: 16365179.