Tumor Necrosis Factor: Cell Survival

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**Important Acronyms**

- TNF-α: Tumor Necrosis Factor (protein)
- TNFR: Tumor Necrosis Factor Receptor
- DD: Death Domain
- SODD: Silencer Of Death Domains
- TRADD: TNF receptor-associated death domain
- TRAF2: TNF-R-associated Factor 2
- RIP: Receptor-interacting protein
- cIPA: Cellular inhibitor of apoptosis
- NFκB : Nuclear Factor κB
- NIK: NFκB-inducing kinase
- IκBα: Inhibitor of NFκB
- IKK: IκBα kinase
• Step 1: The ligand TNF binds to the TNFR and forms a trimer.

• Step 2: SODD is released from the intracellular domain causing a conformational change and allowing the TRADD adaptor proteins to attach.
  o TRADD recruits additional adaptor proteins TRAF2 and RIP
  o TRAF2 recruits cIAP
  o RIP functions as a third arm of the TNF signaling (does not contribute to enzymatic activity of activation of NF-κB)
• Step 3: The \( NF_{\kappa B} \)-inducing kinase (NIK) and RIP phosphorylase and activate the \( I\kappa B\alpha \) (IKK).
  
  o \( I\kappa B\alpha \) becomes degraded by phosphorylation which then leads to activation of \( NF_{\kappa B} \)
  
  o P50/P65 heterodimeric \( NF_{\kappa B} \) then passes into the nucleus
  
  o Once inside, anti-apoptotic genes expression is increased meaning CASP8 and CASP3 activation will be inhibited therefore causing cell survival.

• Step 4: cIAP-1 is cleaved off by Caspase 3- related caspases which leads to an over expression of proteolytic fragments of cIAP-1 which will cause cell death therefore ending the cell survival mechanism.

https://www.mechanobio.info/what-is-mechanosignaling/signaling-pathways/what-is-the-nf-%CE%BAb-pathway/
How this can cause problems

- TNF is a pro-inflammatory cytokine, and chronic inflammation promotes tumor development and progression.
  - TNF could be involved with tumor development and can be used as an indicator of cancer risk, therapy response, and prognosis for cancer patients.
- If a tumor cell is able to follow the phosphorylation cascade rather than the protease cascade this would allow the cancer cell to survive and enter the nucleus and potentially mutating the DNA.
- Finding methods to block the function of anti-apoptotic proteins or increase expression of pro-apoptotic proteins in cancer cells could lead to better drug treatment and development.
Questions?
