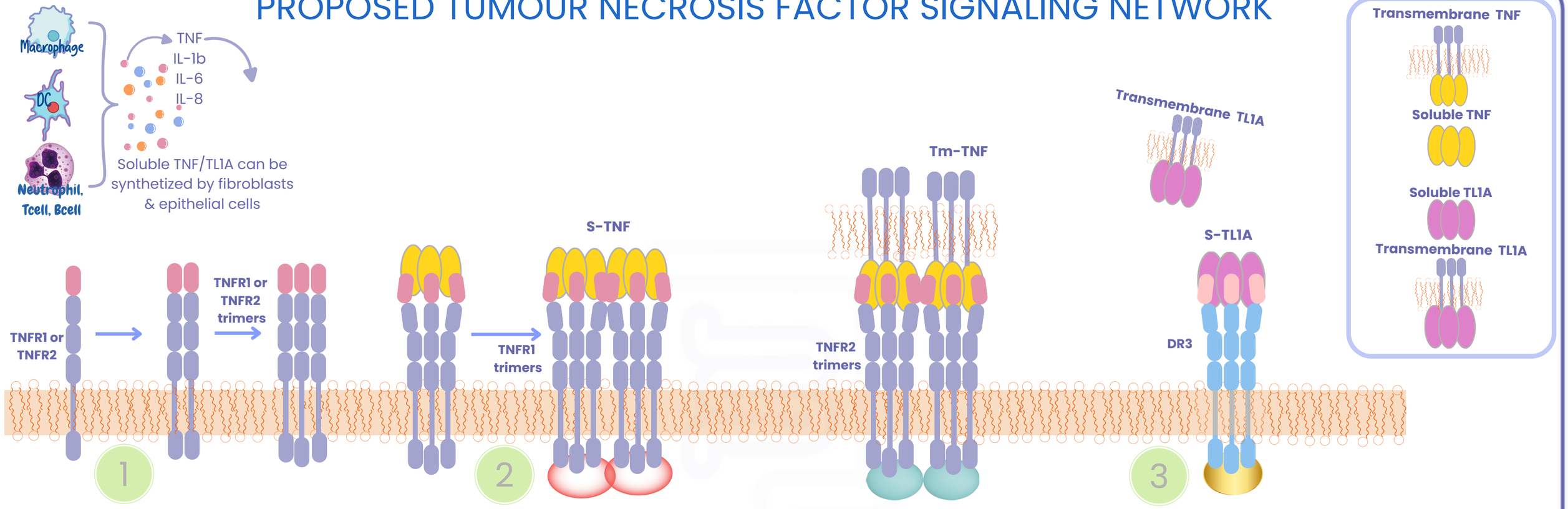
PROPOSED TUMOUR NECROSIS FACTOR SIGNALING NETWORK



1. TNFR1/2 monomers have low affinity for TNF but they spontaneously form trimers that have high affinity.
2. TNF ligand stabilizes TNFR complexes. This allows activation of receptor signaling.
3. DR3 trimer does not need to join to another molecule to be activated.

TNFR1 pathway:

- NF-κB activation & pro-inflammatory cytokines production
- Apoptosis induction via caspase activation
- Insulin resistance & lipolysis in adipose tissue
- Stimulation of hepatic production of acute phase proteins
- Induction of antiviral genes & cellular resistance to viral infection

TNFR2 pathway:

- T cell proliferation & survival
- Enhancement of regulatory Treg function
- Promotion of tissue regeneration & repair
- Neuronal survival & protection in the central nervous system
- Angiogenes stimulation in endothelial cells

TL1A-DR3 pathway:

- T cell activation & proliferation
- Th1 & Th17 cell differentiation
- Treg expansion & function
- Innate lymphoid cell (ILC) activation
- Intestinal inflammation & mucosal immunity
- Bone metabolism regulation
- Direct activation of fibroblasts

Siegmund D et al. Nat Rev Rheumatol. 2023;19(9):576-591
Crof M et al. Nat Rev Drug Discov. 2013 Feb;12(2):147-68.
Palladino MA. Nat Rev Drug Discov.. 2003;2(9):736-46.
Salomon BL. Nat Rev Rheumatol. 2021 ;17(8):487-504.

TNF superfamily is conformed by 19 ligands and 29 receptors. The complexity of TNF pathways far exceeds the capacity of a slide. This is an attempt to condense the most relevant information in IBD field

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