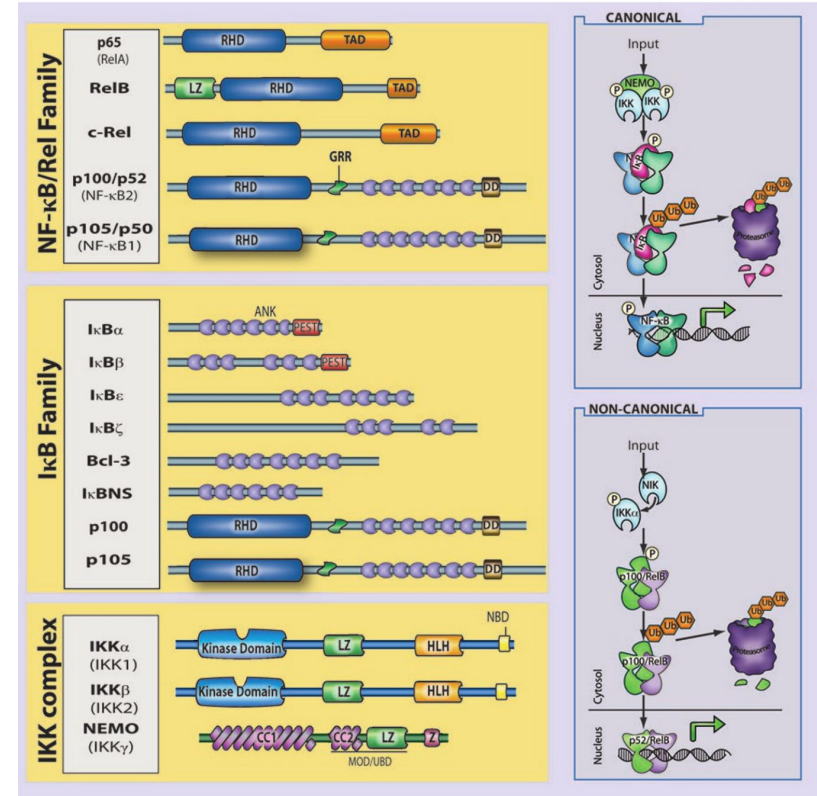


The NF- κ B Transcription Factor Family

Mike Schachter
May 31, 2021

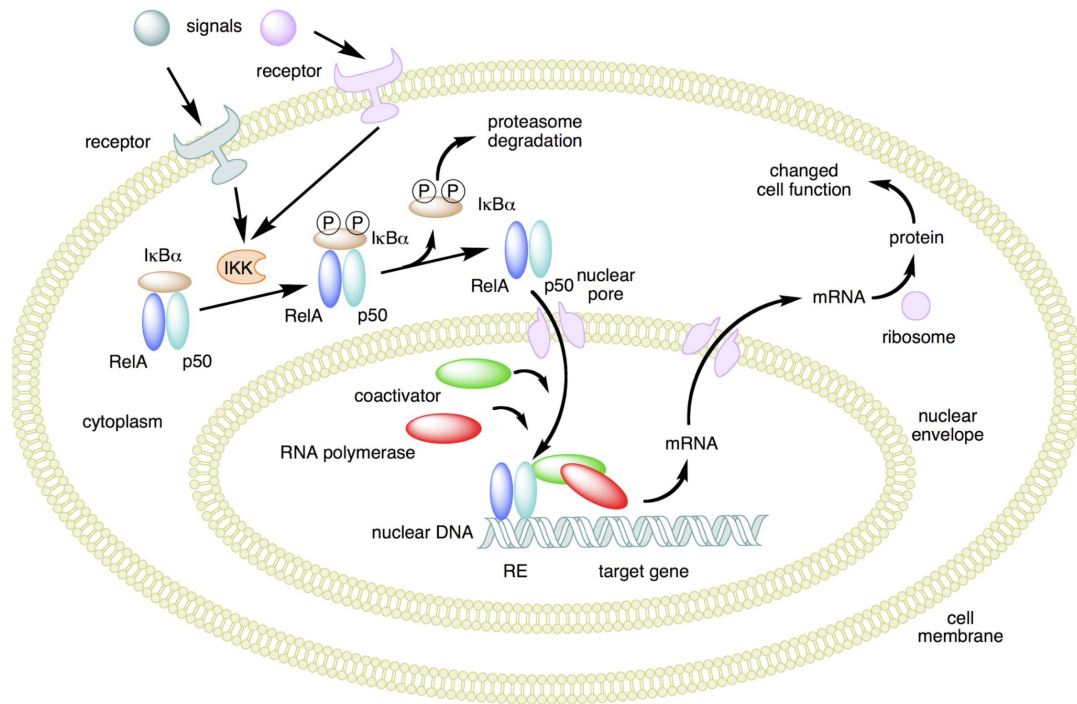
Proteins in the NF-κB Family

- Five proteins in the NF-κB / Rel family:
 - RelA (p65), RelB, c-Rel:** have transcription activation domains (TADs) and can directly promote transcription.
 - p50 = cleaved NFKB1 (p105)**
 - p52 = cleaved NFKB2 (p100)**
- NF-κB proteins form homo- and heterodimers, **p50/RelA** is most common.
- NF-κB proteins are already transcribed, in the cytoplasm and “ready to go”, but inhibited by **IκB proteins**.
- IKK proteins** sense pathogen activity or cellular damage and phosphorylate IκB, freeing NF-κB to translocate to the nucleus.



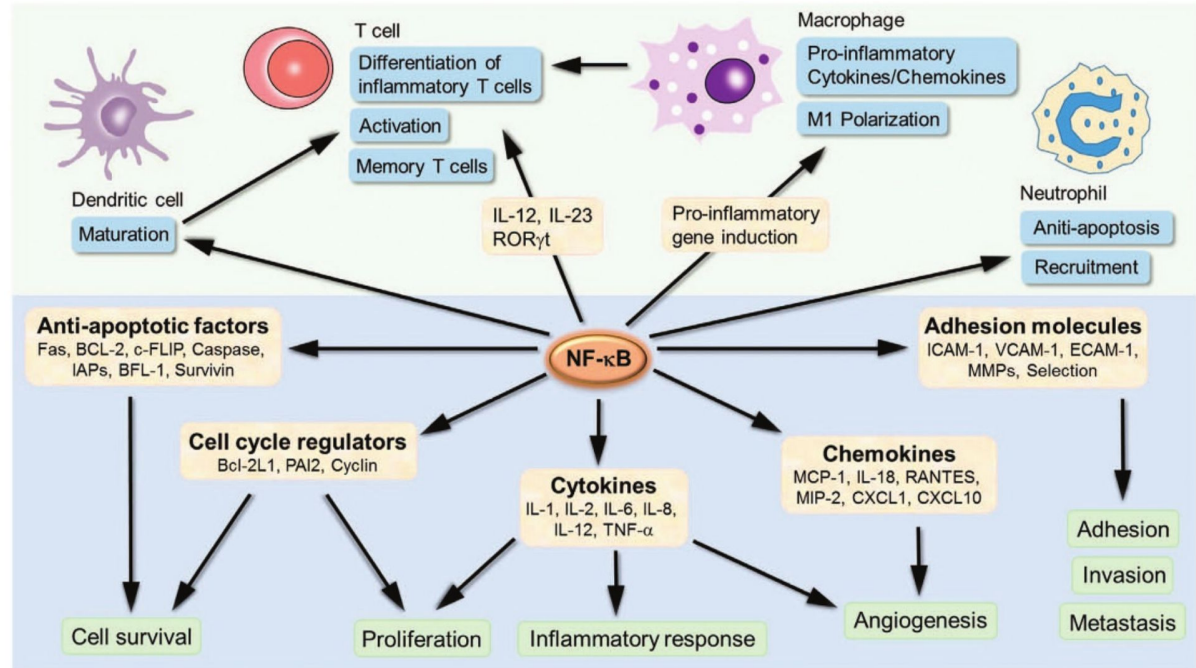
An Example NF- κ B pathway

1. Cellular damage and pathogen activity stimulate receptors.
 2. Those receptors activate IKKs.
 3. IKKs dis-inhibit an NF- κ B dimer by phosphorylating an I κ B.
 4. The NF- κ B dimer translocates to the nucleus and promotes or inhibits transcription.
- Dimers with Rel, RelA, or RelB **promote** transcription.
 - Homodimers of p50 **inhibit** transcription.



Cellular Functions Promoted by NF- κ B

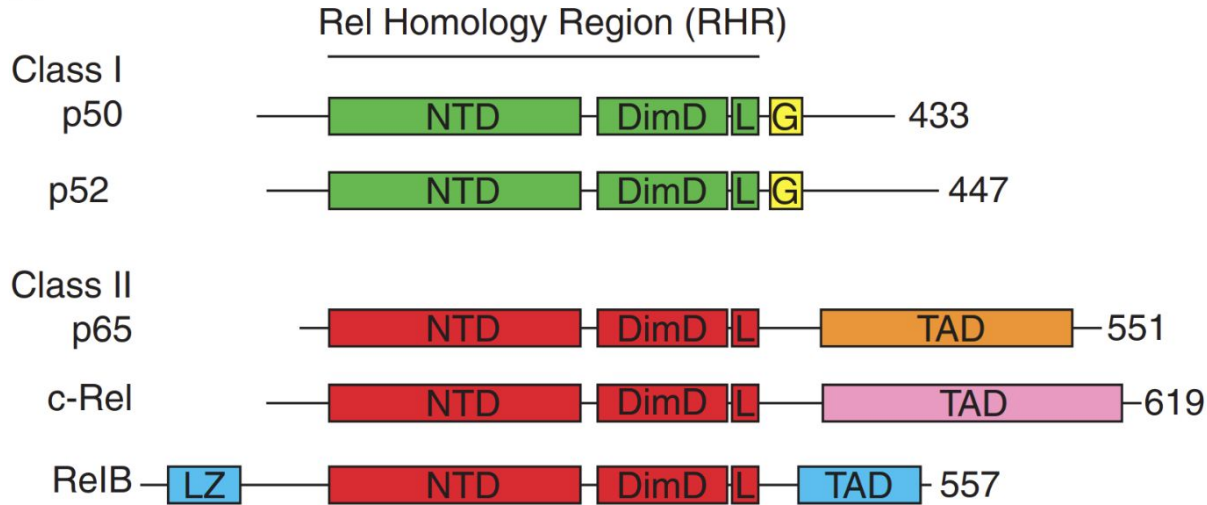
- Best known for promoting **inflammatory response** to cellular damage and pathogens.
- Dysfunction can promote **cancer** or **immune disorders**.



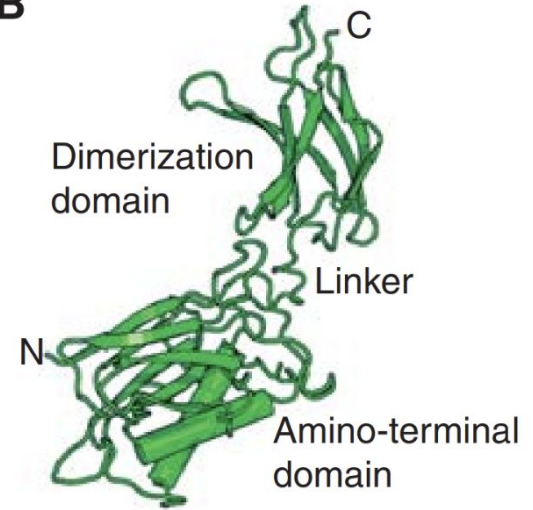
Liu, T., Zhang, L., Joo, D., & Sun, S. C (2017) NF- κ B signaling in inflammation. *Signal Transduct Target Ther*, 2, 17023.

Structure of Rel-Homology Region

A



B

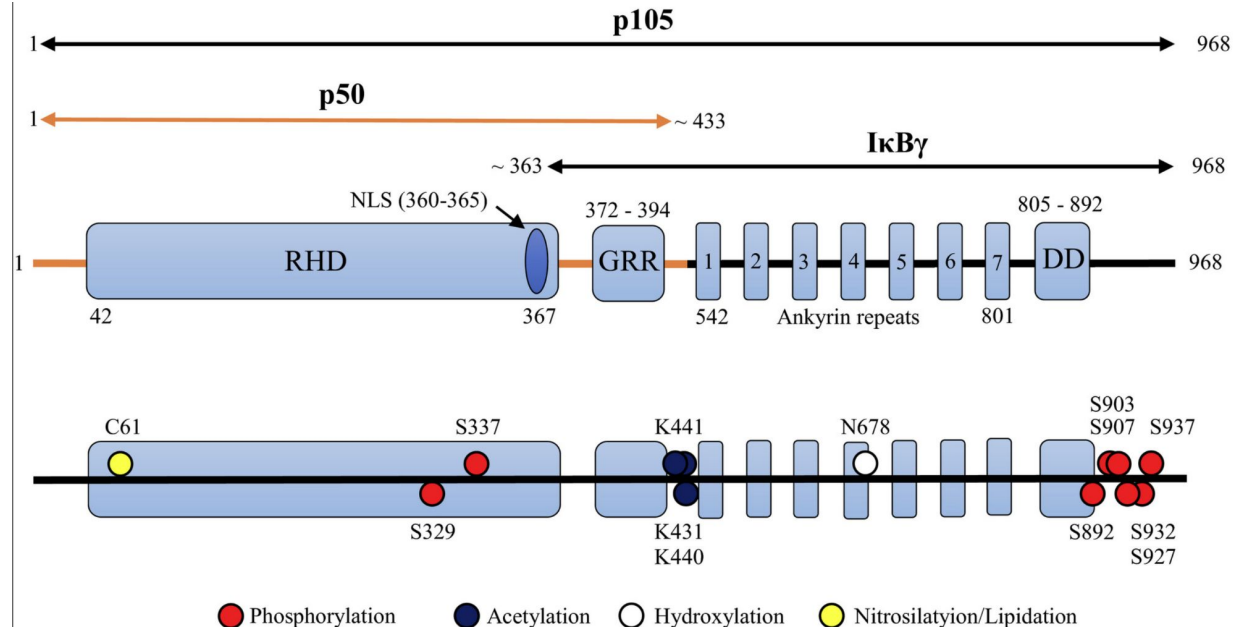


- NF- κ B proteins share a common Rel Homology region (or domain, “RHR” or “RHD”)
- The region has sub-structures for dimerization and binding to DNA.

Huxford, T., & Ghosh, G. (2009). A structural guide to proteins of the NF- κ B signaling module. *Cold Spring Harbor perspectives in biology*, 1(3), a000075.

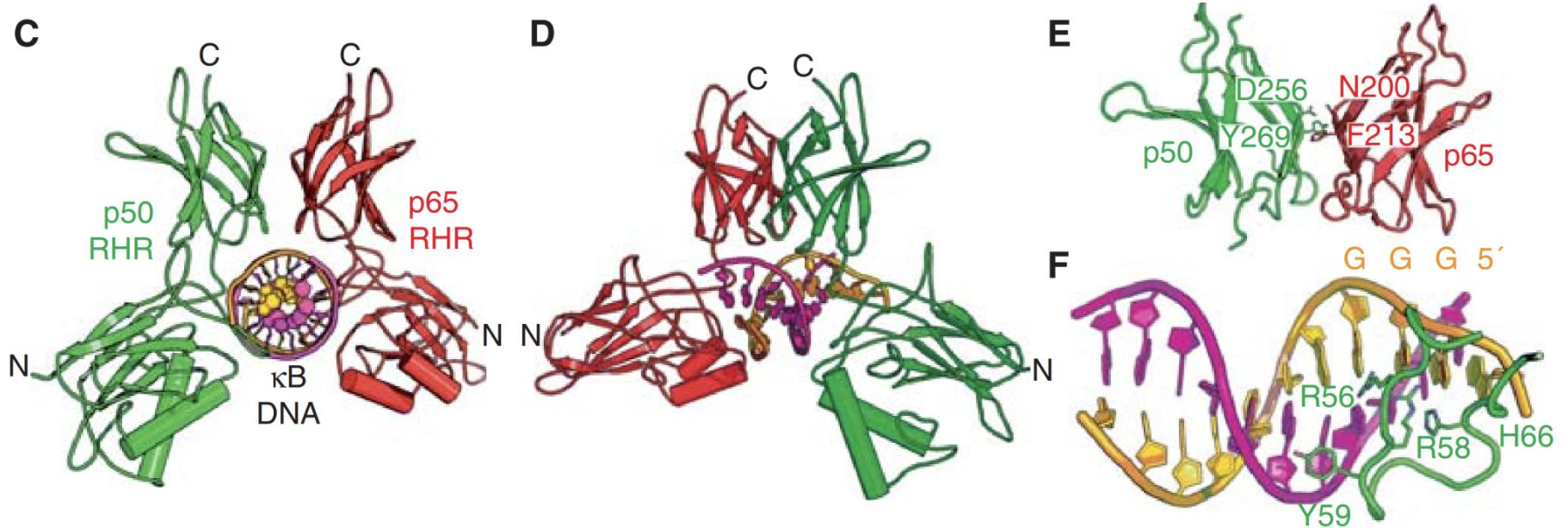
NFKB1/p105 Structural Schematic

- NFKB1 is transcribed as a 105kD protein with 968 amino acids, called p105.
- p105 can be cleaved by a proteasome into p50.
- p50 forms homodimers that repress transcription, may produce anti-inflammatory effects.



Cartwright, T., Perkins, N. D., & Wilson, C. L. (2016). NFKB1: a suppressor of inflammation, ageing and cancer. *The FEBS journal*, 283(10), 1812-1822.

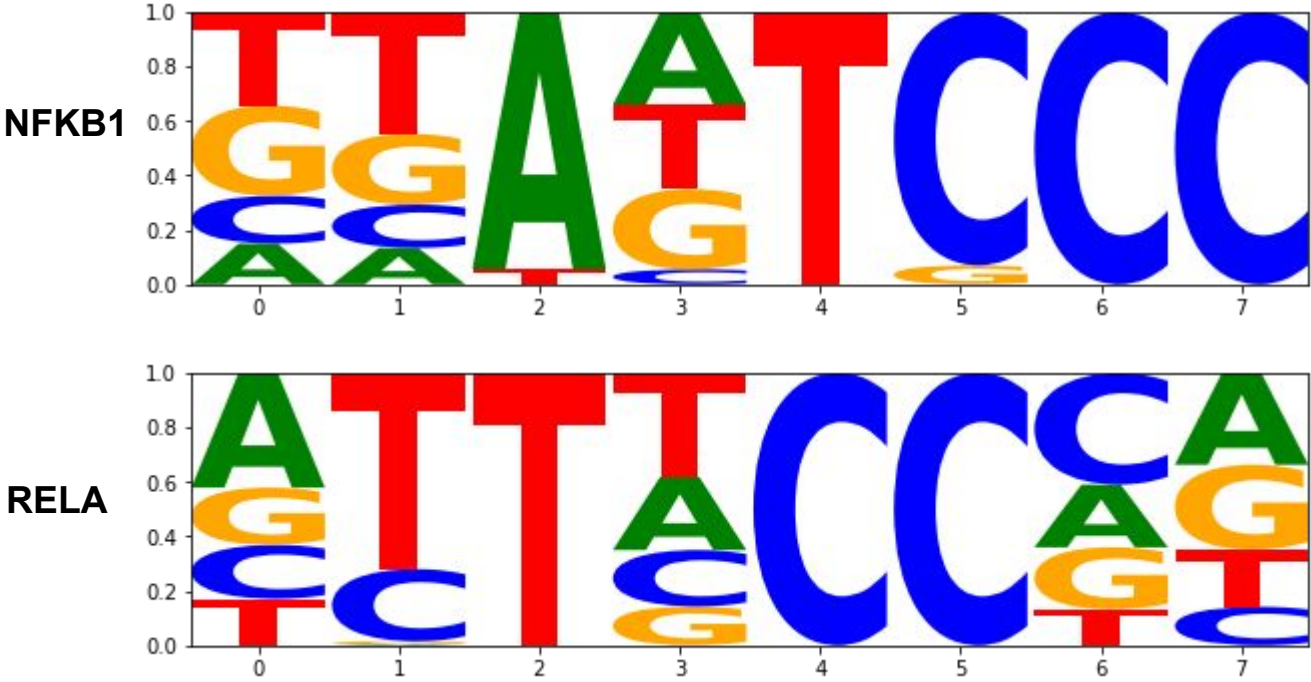
Rel-Homology Region Binding to DNA



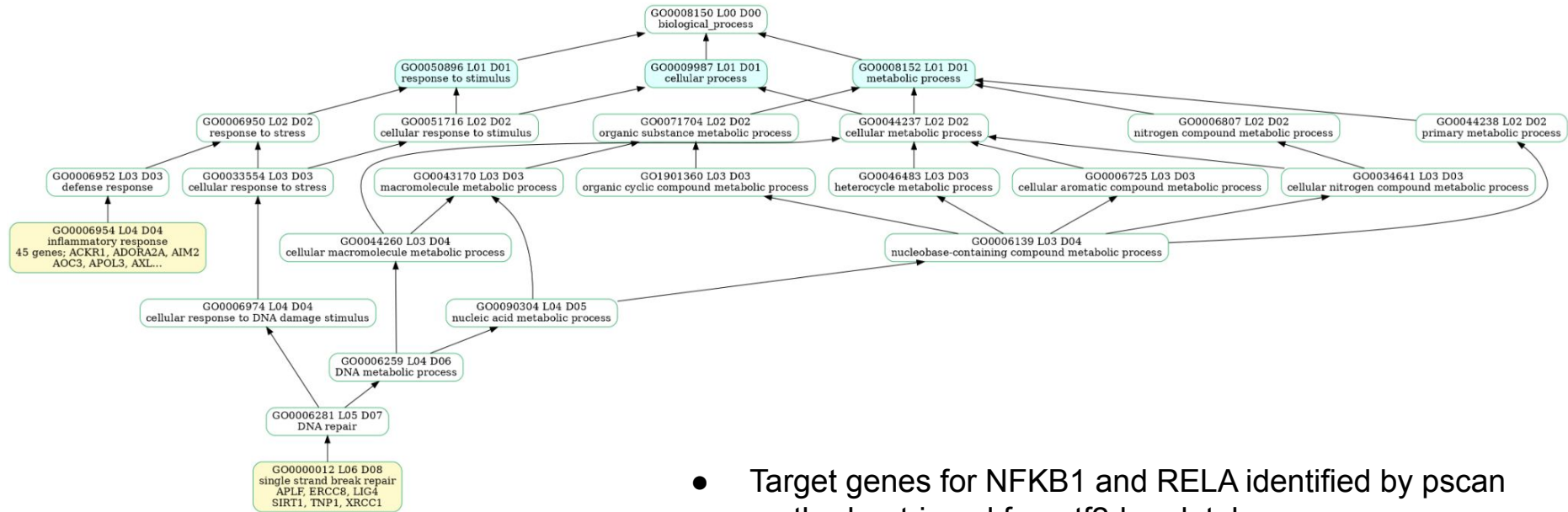
- X-ray crystallography studies suggest DNA binding is achieved by residues near the N-terminal in the linker region.

Huxford, T., & Ghosh, G. (2009). A structural guide to proteins of the NF-κB signaling module. *Cold Spring Harbor perspectives in biology*, 1(3), a000075.

Transcription Factor Binding Motifs



Ontology Analysis of Gene Targets



- Target genes for NFKB1 and RELA identified by pscan method, retrieved from tf2dna database.
- Genes with p value < 1e-5 retained.
- Ontology analysis performed for retained genes with GOATOOLS.

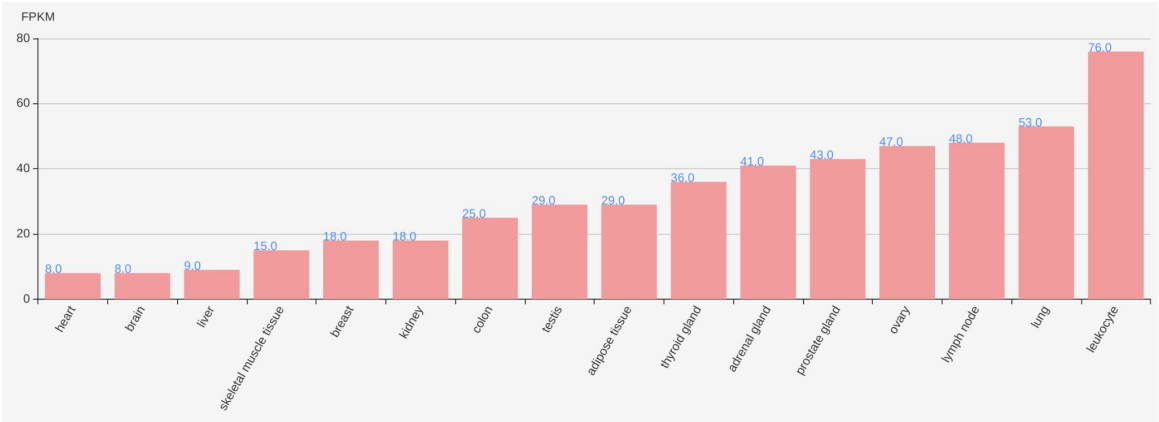
Ontology Analysis of Gene Targets

- Also run through geneontology.org.
- Results confirm consensus findings that NF- κ B pathway:
 - Responds to cytokine stimulation.
 - Involved in cellular differentiation.
 - Responds to cellular damage.

single strand break repair (GO:0000012)
interferon-gamma-mediated signaling pathway (GO:0060333)
cellular response to chemokine (GO:1990869)
regulation of type I interferon production (GO:0032479)
inflammatory response (GO:0006954)
regulation of response to external stimulus (GO:0032101)
regulation of response to stress (GO:0080134)
regulation of immune system process (GO:0002682)
cell differentiation (GO:0030154)

Tissue-specific Expression Profiles

NFKB1/p105



RELA/p65

