

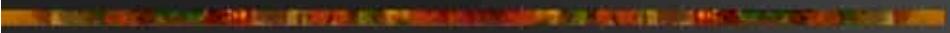


On the TRAIL to Tumor Apoptosis



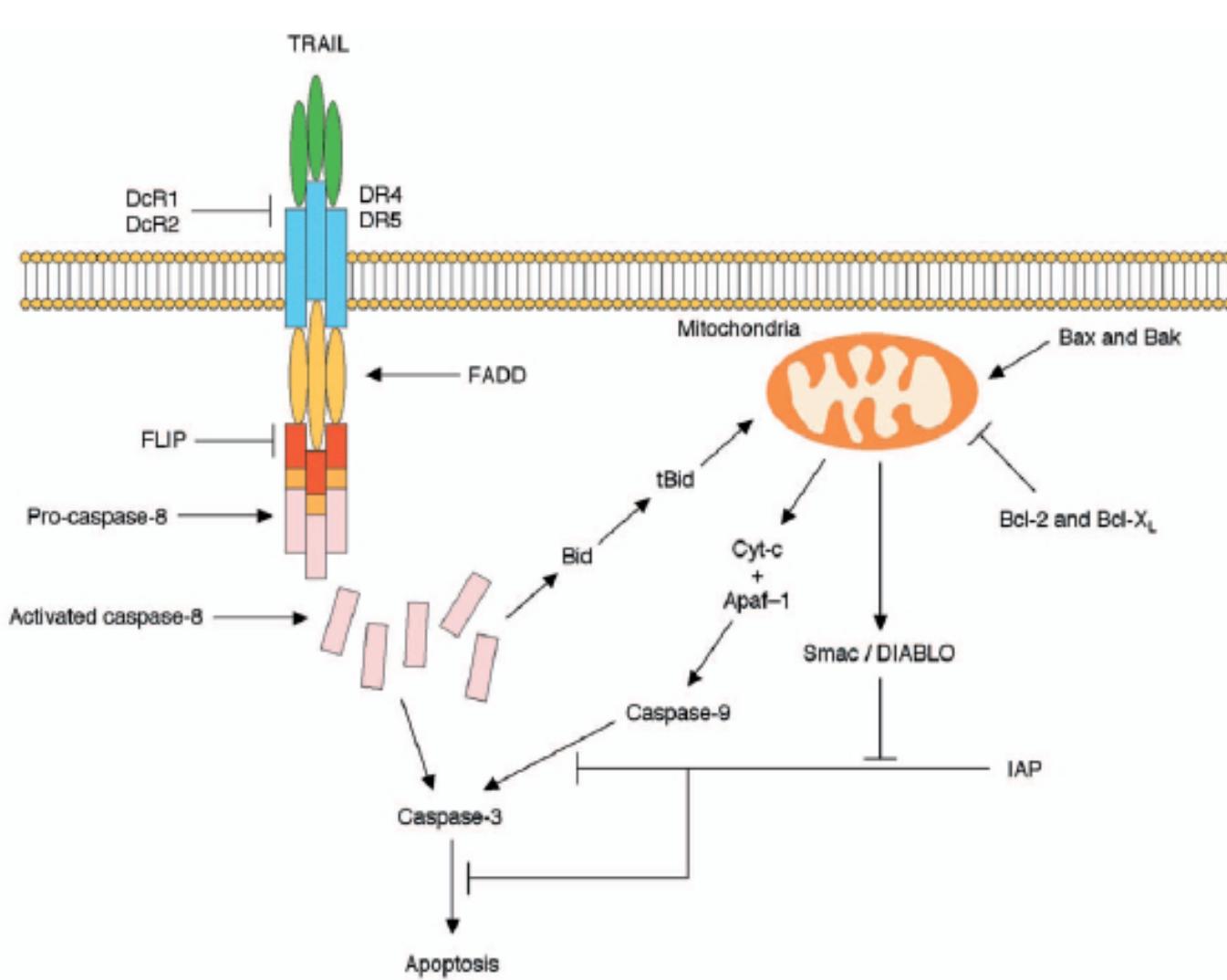
Jeffrey L. Martin
12 Dec 2005

The Story



- Tumor necrosis factor (TNF) receptors
 - Involved in apoptosis pathway
- TRAIL
 - Homotrimer
 - TNF ligand
 - Binds specifically to tumor cells
 - Binding causes trimerization of TNF receptors
 - Signals for cell apoptosis
 - Known targets: DR4, DR5, DcR1, DcR2



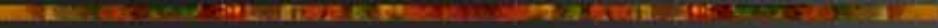


Cell Apoptosis Pathway

Good 'OI Structure

- Resolution: 2.2Å
- R factor: 22.1%
- R_{free} : 27.0%
- Unique reflections: 18,029

The All-Stars



- Arg 149 containing loop
 - Mutation (SLL)
- Gln205, Tyr216, Glu236, Tyr237
 - Alanine substitutions
 - Gln205 and Tyr 216
 - Arg 158 and Tyr 237

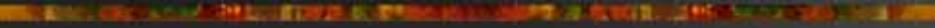


The MVP



- Three Cys 230 proximal at trimer interface
 - Mutation to Ala or Ser
 - 70 fold reduction in activity
 - Form disulfide bonds?
 - Yes, but that's not all!

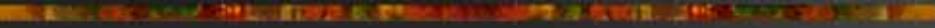
Overrated or a True Star?



- Zinc? That's a first!
- Take 'em out!
 - 90-fold decrease in activity
 - Reduction in β -sheet content
 - Tryptophan fluorescence reduction
 - Only two Trp residues conserved: 154, 231
 - Melting temperature 25°C lower



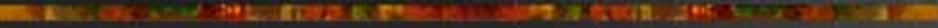
To Sum It Up



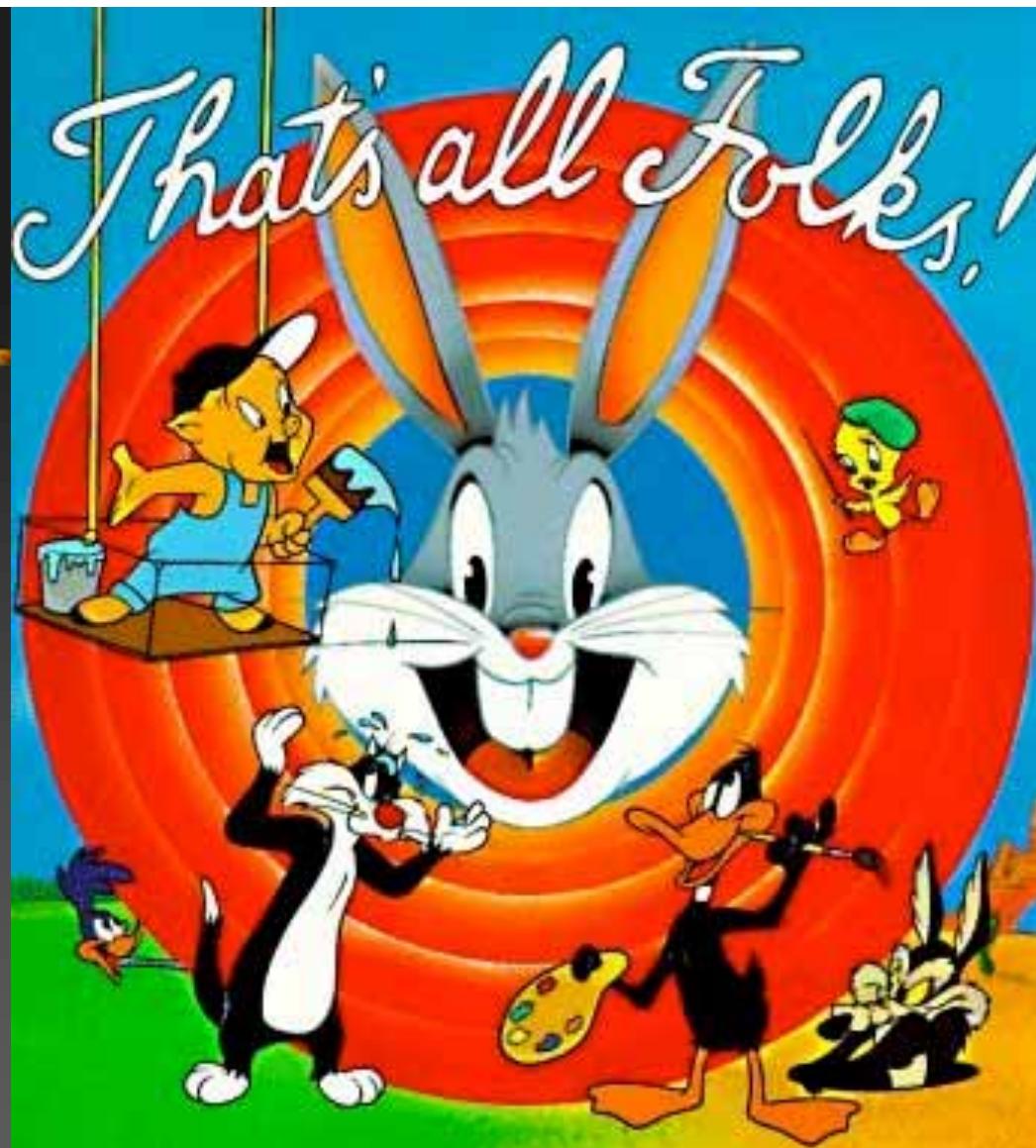
- Trail uses many weaker interactions
 - Different mutation combinations for targeting
 - A promising drug model
- Zinc site
 - Only TNF ligand with a metal site
 - Contributes to protein stability



References



- Yagita H. TRAIL and its receptors as targets for cancer therapy. *Cancer Sci* 2004, 95, 777-783.
- Screamton et al. Structure of the TRAIL-DR5 complex reveals mechanisms conferring specificity in apoptotic initiation. *Nat. Struct. Biol.* 1999, 9, 1048-1053
- Hymowitz et al. A Unique Zinc-Binding Site Revealed by a High-Resolution X-Ray Structure of Homotrimeric Apo2L/TRAIL. *Biochemistry*, 2000, 39, 633-640.



The Art of Warner Bros. Animation

By Steve Schneider

Foreword by Ray Bradbury