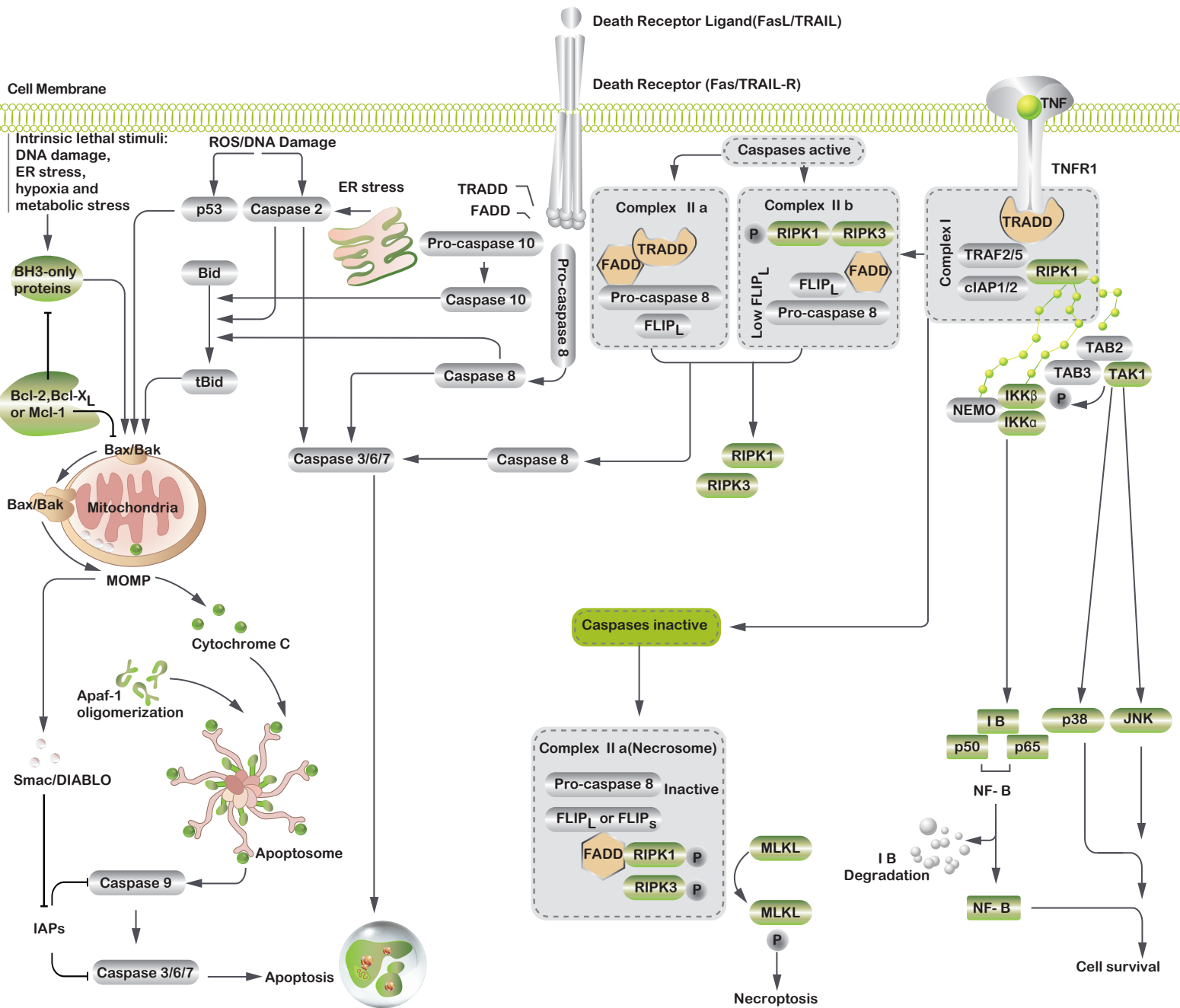


TNF and Apoptosis Signaling



TNF (Tumor Necrosis Factor) is a multifunctional proinflammatory cytokine, which has been considered as an anti-cancer agent since its discovery two decades ago. Besides TNF, TNF superfamily proteins consist of other 18 members, acting through 29 receptors that belong to the TNF receptor (TNFR) superfamily. Members of the TNFR super family can send both survival and death signals to cells.

Following the binding of the death ligand to Death Receptors (DRs), including FasL, TNF-, and TRAIL, on the plasma membrane, the DR, adaptor protein (FADD), and associated apoptosis signaling molecule (caspase-8) form the death-inducing signaling complex (DISC), thus leading to the activation of the effector caspase cascade (caspase 3, 6, and 7). This is called extrinsic apoptosis pathway. Following the binding of TNF to TNFR1, TNFR1 binds to TRADD, which recruits RIPK1, TRAF2/5 and cIAP1/2 to form TNFR1 signaling complex I. The Pro-caspase 8 homodimer in complex IIa and complex IIb generates active caspase 8. This active caspase 8 in the cytosol then carries out cleavage reactions to activate downstream executioner caspases and thus induce classical apoptosis. When caspase 8 is inactivated, Necroptosis, an alternative type of regulated cell death, will occur following the formation of Necrosome, which includes RIP1, RIP3, and its substrate, mixed lineage kinase domain like pseudokinase (MLKL). Upon binding to TNFR1 or TNFR2 (not shown), TNF may also activate the NF- κ B pathway via IKK. The activation of NF- κ B induces the expression of pro-survival genes including Bcl-2 and FLIP, the latter can directly inhibit the activation of caspase-8.

Some intrinsic stimuli (e.g. ROS/DNA damage and ER stress) will also trigger mitochondria-mediated intrinsic apoptosis pathway, which is regulated by Bcl-2 family proteins, including proapoptotic (Bid, Bax, Bak) and antiapoptotic proteins (Bcl-2, Bcl-x_L). Caspase 2, 8 and 10 can also cleave Bid, lead to mitochondrial outer membrane permeabilization (MOMP). Following MOMP, mitochondrial intermembrane space proteins such as Smac and Cytochrome C are released into the cytosol. Cytochrome C interacts with Apaf-1, triggering apoptosome assembly, which activates Caspase 9. Active caspase 9, in turn, activates caspase 3, 6 and 7, leading to apoptosis. Mitochondrial release of Smac facilitates apoptosis by blocking the inhibitor of apoptosis (IAP) proteins.

Key Products for TNF and Apoptosis Signaling

Target Name	Cat.No.	Reactivity	Applications	Citations
TNFR1	bs-2941R	Human,Mouse,Rat	WB,FCM	PubMed
TNFR2	bs-16610R	Human,Mouse	WB,FCM	
FAS/CD95	bs-0215R	Human,Mouse,Rat	IHC-P,FCM	PubMed
Fas Ligand	bs-0216R	Human,Mouse,Rat	WB,IHC-P,FCM,IF	PubMed
TRAIL	bs-1214R	Human,Mouse,Rat	WB,IHC-P	PubMed
FADD	bs-0511R	Human,Mouse,Rat	WB,IHC-P	PubMed
TRADD	bs-1202R	Human,Mouse,Rat	WB,IHC-P	PubMed
Bak	bs-1284R	Human,Mouse,Rat	WB,IHC-P,FCM	PubMed
Bax	bs-0127R	Human,Mouse,Rat	WB,IHC-P,FCM	PubMed
Bcl-2	bs-0032R	Human,Mouse,Rat	WB,IHC-P,FCM,IF	PubMed
Bcl-xL	bs-1336R	Human,Mouse,Rat	WB,IHC-P,FCM	PubMed
Bim	bs-1488R	Human,Mouse,Rat	WB,FCM	
Phospho-Bax (Ser184)	bs-3010R	Human,Mouse,Rat	WB,FCM	PubMed
Phospho-Bcl-2 (Thr129)	bs-5220R	Human,Mouse,Rat	WB,IHC-P,FCM	
Phospho-Bcl-xL (Thr115)	bs-5234R	Human,Mouse,Rat	WB,IHC-P	
Phospho-Bcl-xL (Thr47)	bs-12579R	Human,Mouse,Rat	WB,IHC-P	
Phospho-Bim (Ser55)	bs-3058R	Human,Mouse,Rat	WB,IHC-P	
Phospho-Bim (Ser87)	bs-3012R	Human,Mouse,Rat	WB,IHC-P	PubMed
caspase-8 subunit p18	bs-6463R	Human,Mouse,Rat	WB,IHC-P	PubMed
Caspase-9	bs-0049R	Human,Mouse,Rat	WB,IHC-P,FCM	
Caspase-10	bs-23454R	Human	WB,IHC-P	
Caspase-12	bs-1105R	Mouse,Rat	WB,IHC-P	
Caspase-3	bs-0081R	Human,Mouse,Rat	WB,IHC-P,FCM	PubMed
caspase-3 p12 subunit	bs-0087R	Human,Mouse,Rat	IHC-P,FCM	PubMed
caspase-6 p18 subunit	bs-0084R	Human,Mouse,Rat	WB,IHC-P,IF	
Caspase-7 p20 subunit	bs-3665R	Human,Mouse,Rat	WB,IHC-P	
Cytochrome C	bs-0013R	Human,Mouse,Rat	WB,IHC-P	PubMed
Survivin	bs-0615R	Human,Mouse,Rat	WB,IHC-P,FCM	PubMed
FLIP	bs-0119R	Human,Mouse,Rat	WB,IHC-P,FCM	
cIAP	bs-4262R	Human,Mouse,Rat	WB	
XIAP	bs-1281R	Human,Mouse,Rat	WB,FCM	PubMed
IKK alpha + IKK beta	bs-10123R	Human,Mouse,Rat	WB,IHC-P	
Phospho-IKK alpha/beta (Ser176 + Ser180)	bs-3237R	Human,Mouse,Rat	WB,IHC-P	PubMed
JNK1+JNK2+JNK3	bs-2592R	Human,Mouse,Rat	WB,IHC-P,FCM	PubMed
Phospho-JNK1 + 2 + 3 (Thr183+Tyr185)	bs-1640R	Human,Mouse,Rat	WB,IHC-P,FCM	PubMed
P38 MAPK	bs-0637R	Human,Mouse,Rat	WB	PubMed
Phospho-P38 MAPK (Thr180 + Tyr182)	bs-0636R	Human,Mouse,Rat	WB	PubMed
NFκB p65	bs-20355R	Human,Mouse,Rat	WB,IHC-P,FCM	
Phospho-NFκB p65 (Ser536)	bs-0982R	Human,Mouse,Rat	WB,IHC-P,FCM	PubMed
RIPK1	bs-5805R	Human,Mouse,Rat	WB,IHC-P	PubMed
RIPK3	bs-3551R	Human,Mouse,Rat	WB,IHC-P	PubMed
MLKL	bsm-33339M	Human,Mouse,Rat	WB,IHC-P	
Phospho-MLKL (Ser358)	bsm-33331M	Human,Mouse,Rat	WB,IHC-P	

WB=Western Blot; IHC-P=Immunohistochemistry with Paraffin-Embedded Tissue Slides; IF=Immunofluorescence; FCM=Flow cytometry