SUPPLEMENTARY MATERIAL

Mathematical Modelling of Cell-Fate Decision in Response to Death Receptor Engagement

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GINsim REPORT OF THE ANNOTATED MODEL

ID	Value	Logical function	Comment
FASL	1	FASL:1	
TNF	1	TNF:1	
TNFR	1	TNF:1	TNFR represents the engagement of TNF receptor by TNF.
DISC-TNF	1	FADD:1 & TNFR:1	DISC-TNF (TNF complex II) is a protein complex that acts as a signalling platform that assembles following TNFR1 engagement. It is composed of TRADD, TRAF2, FADD and caspase-8 but not TNFR1 [1].
DISC-FAS	1	FASL:1 & FADD:1	DISC-FAS is a protein complex that acts as a signalling platform. It is formed by recruitment of at least FADD and pro-CASP8 at the intracellular domain of FAS following engagement of FAS by FASL [2].
FADD	1	FADD:1	FADD represents the presence of protein FADD, that acts as an adaptor in death domain receptors complexes TNF-complex II (DISC-TNF) [1] and DISC-FAS [2]. FADD:0 represents conditions of genetic invalidation of FADD.
RIP1	1	(DISC-FAS:1 | TNFR:1) & !CASP8	RIP1 represents the recruitment of RIP1 protein to death receptor associated complexes TNFR1-complex I [1] and DISC-FAS [3,4]. Active CASP8 cleaves RIP1, leading to inhibition of NFkB mediated antiapoptotic signalling [5,6] and RIP1-mediated necrosis [7].
RIP1ub	1	cIAP:1 & RIP1:1	RIP1ub represents the K63-linked ubiquitin conjugation of RIP1. IAPs act as a RIP1 E3-ubiquitin ligases. [8,9]
RIP1K	1	RIP1:1	RIP1K represents to the kinase activity of RIP1 FAS triggers a caspase-8-independent cell death pathway using the kinase RIP as effector molecule. The kinase activity of RIP1 is indispensable [3].
IKK	1	RIP1ub:1	RIP1 K63-ubiquitinated within complex I recruits member of the IKK complex NEMO upstream of NF-kB activation [5]. RIP mediates the TNF-induced [10] and FAS-induced [4] NFkB activation. The kinase activity of RIP1 is not required for TNF-induced IKK activation [11].
NFkB	0 1	CASP3:1 IKK:1 & !CASP3	In the so-called canonical pathway, NFkB is activated by release from its inhibitor IkB, which arises following IKK mediated phosphorylation of IkB [12]. Several components in the canonical NFkB activation pathway are substrates for CASP3-mediated proteolysis

			[13].
CASP8	0 1	cFLIP (DISC-TNF | DISC-FAS | CASP3:1) & !cFLIP	cFLIP inhibits the activation of caspase-8 at the receptor level [14]. TNF complex II recruits CASP8 which leads to its activation [1]. CASP8 is activated by self-cleavage upon recruitment into the DISC-FAS complex [15,16]. In a positive feed-forward amplification loop, CASP3 proteolytically activates CASP8, with CASP6 possibly acting as an intermediate in this process [17,18].
BAX	0 1	BCL2:1 CASP8:1 & !BCL2	BAX represents BAX (or BAK) activation by insertion into the outer membrane of mitochondria and oligomerization. Anti-apoptotic BH3 family members such as BCL2 inhibits BAX/BAK activation by direct interactions and/or by sequestration of pro-apoptotic BH3-only proteins [19]. CASP8-truncated Bid [20] induces the oligomerization of BAX and BAK and the formation of pores into the outer membrane of mitochondria [21].
BCL2	1	NFkB:1	BCL2 [22] and other anti-apoptotic BH3 family members such as Bfl1 [23] or BCL-xL [24] are NFkB target genes.
ROS	1	!NFkB & (MPT:1 | RIP1K:1)	RIP1 initiates caspase-independent necrosis pathway mediated by the ROS [7]. ROS are produced by NADPH oxidases activated downstream of TRADD, RIP1 and RAC1 [25]. NFkB target genes include antioxidants such as SOD2 [26] or FHC [27] that protect cell through ROS inhibition.
ATP	1	!MPT	Necrosis is accompanied by total depletion of ATP, as the result of the loss of $\Delta\psi m$ [28]
MPT	1	!BCL2 & ROS:1	By opposition to MOMP, MPT represents the permeabilization of necrotic mitochondria, as proposed by [29]. ROS production downstream of RIP1 kinase activation is involved in necrosis induction [30], and can target the permeability transition pore complex for MPT induction [29]. BCL2 over-expression inhibits MPT, probably through direct interaction with the permeabilization transition pore comple [31].
MOMP	1	BAX:1 | MPT:1	BAX/BAK pore formation at the outer membrane of mitochondria induces the release of intermembrane space resident proteins into the cytosol [21]. During TNF-induced necrotic cell death, MPT can lead to

			membranes disruption and release of intermembrane space resident proteins into the cytosol [29]
SMAC	1	MOMP	SMAC is released during MOMP in the cytosol [32].
cIAP	0 1	SMAC:1 (NFkB:1 | cIAP:1) & !SMAC	cIAP stands for cIAP1 or cIAP2 SMAC promotes the auto-ubiquitination and degradation of the cIAPs [8]. cIAPs are NFkB target genes [33]. Self-regulation on cIAP is introduced to allow cIAP:1 even if NFkB:0.
Cyt_c	1	MOMP	Cyt_c represents the release of cytochrome c from the mitochondria. Cyt_c is localized in the mitochondrial intermembrane space and is part of the mitochondrial electron transport chain. It is released in the cytosol during apoptosis [21].
XIAP	1	!SMAC & NFkB:1	SMAC, once released in the cytosol, inactivates caspase inhibitor XIAP [32]. XIAP is a NFkB target gene [34].
apoptosome	0 1	XIAP:1 Cyt_c:1 & ATP & !XIAP	XIAP is an inhibitor of CASP9 [35]. Once released in the cytosol, Cyt_c assembles in a ATP/dATP-dependent manner with Apaf1, and pro-caspase 9 to form the apoptosome complex [36].
CASP3	0 1	XIAP:1 apoptosome & !XIAP	XIAP acts as a CASP3 inhibitor [32]. Activated CASP9 in the apoptosome complex induces proteolytic activation of executioner caspases [36].
cFLIP	1	NFkB:1	cFLIP is a target gene of NF-kB [37].
NonACD	1	!ATP	Necrosis is usually accompanied by total depletion of ATP [28].
Apoptosis	1	CASP3	Cleavage of executioner caspases substrates such as ICAM [38] or PARP1 [39] is considered as the execution phase of apoptosis.
Survival	1	NFkB:1	NFkB activation is considered the marker for survival.

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