Death receptor signaling

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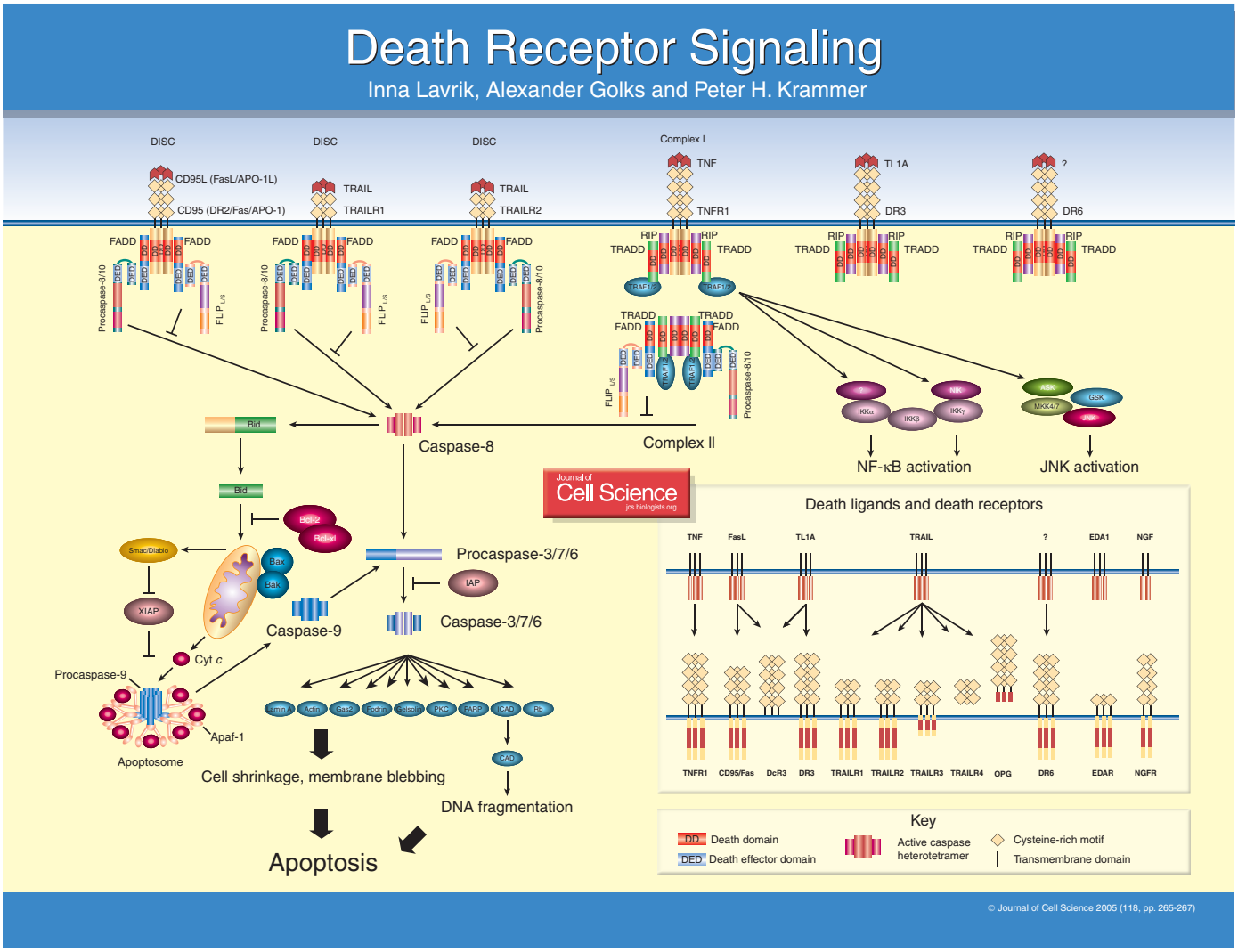
Apoptosis or programmed cell death is a common property of multicellular organisms (Danial and Korsmeyer, 2004; Krammer, 2000). It can be triggered by a number of factors, including UV- or γ-irradiation, chemotherapeutic drugs or signaling by death receptors (DR). The DR family is part of the tumor necrosis factor receptor superfamily (Bhardwaj and Aggarwal, 2003). Triggering members of the DR family by death ligands results in the transduction of either apoptotic or survival signals. The poster shows a general overview of DR signaling, summarizing the molecules and pathways involved.

Death receptor family members

Eight members of the death receptor family have been characterized so far: tumor necrosis factor receptor 1 (TNFR1; also known as DR1, CD120a, p55 and p60), CD95 (also known as DR2, APO-1 and Fas), DR3 (also known as APO-3, LARD, TRAMP and WSL1), TNF-related apoptosis-inducing ligand receptor 1 (TRAILR1; also known as DR4 and APO-2), TRAILR2 (also known as DR5, KILLER and TRICK2), DR6, ectodysplasin A receptor (EDAR) and nerve growth factor receptor (NGFR) (French and Tschopp, 2003; Wajant, 2003). These are distinguished by a cytoplasmic region of ~80 residues termed the death domain (DD). When these receptors are triggered by corresponding ligands, a number of molecules are recruited to the DD and subsequently a signaling cascade is activated. Death ligands also interact with decoy receptors (DcRs) that do not possess DDs and so cannot form signaling complexes. To date, four decoy receptors have been characterized: TRAILR3 (also known as DcR1), TRAILR4 (also known as DcR2), DcR3 and osteoprotegrin (OPG).

Two types of DR signaling complex can be distinguished. The first group comprises the death-inducing signaling



(See poster insert)

complexes (DISCs) that are formed at the CD95 receptor, TRAILR1 or TRAILR2 (Peter and Krammer, 2003). All three receptors recruit DISCs with similar compositions. DISC formation results in the activation of caspase-8, which plays the central role in transduction of the apoptotic signal. The second group comprises the TNFR1, DR3, DR6 and EDAR. These recruit a different set of molecules, which transduce both apoptotic and survival signals.

CD95/Fas and TRAILR signaling

CD95 and TRAILR1/TRAILR2 DISCs consist of oligomerized, probably trimerized, receptors, the DD-containing adaptor molecule FADD (Fas-Associated Death Domain), two isoforms of procaspase-8 (procaspase-8/a and procaspase-8/b), procaspase-10 and the cellular FLICE-inhibitory protein ($FLIP_{L/S}$) (Peter and Krammer, 2003). The interactions between the molecules at the DISC are based on homotypic contacts. The DD of the receptor interacts with the DD of FADD whereas the death effector domain (DED) of FADD interacts with the N-terminal tandem DEDs of procaspase-8, procaspase-10 and $FLIP_{L/S}$. Activation of procaspase-8 is believed to follow an 'induced proximity' model, in which high local concentrations of procaspase-8 at the DISC lead to its autoproteolytic activation, a multi-step cleavage process resulting in formation of a caspase-8 heterotetramer containing two large subunits (p18) and two small subunits (p10). This is then released into the cytosol to propagate the apoptotic signal.

Procaspase-10 is also activated at the DISC, forming an active heterotetramer (Sprick et al., 2002). However, whether caspase-10 can trigger cell death in absence of caspase-8 in response to CD95 or TRAILR1/R2 stimulation is controversial. Thus, the role of caspase-10 remains elusive.

$FLIP_L$ and $FLIP_S$ inhibit activation of procaspase-8 at the DISC by blocking its processing. There is increasing evidence that $FLIP_L$ also facilitates the cleavage of procaspase-8 at the DISC by forming $FLIP_L$–procaspase-8 heterodimers (Chang et al., 2003; Micheau et al., 2002). A detailed understanding of FLIP action at the DISC requires further studies.

Besides the above-mentioned components of the DISC, a number of molecules have been reported to be recruited to the DISC by direct interaction with DISC proteins (Daxx, FAP-1, FLASH, RIP, FAF-1 and others). The roles of many of these proteins are unclear (Peter and Krammer, 2003).

Two types of CD95 signaling have been established. Type I cells are characterized by high levels of DISC formation and increased amounts of active caspase-8. Activated caspase-8 directly leads to the activation of downstream effector caspases. In type II cells, there are lower levels of CD95 DISC formation and, thus, lower levels of active caspase-8 (Scaffidi et al., 1998). In this case, signaling requires an additional amplification loop that involves the cleavage by caspase-8 of the Bcl-2-family protein Bid to generate truncated (t) Bid and subsequent tBid-mediated release of cytochrome *c* (Cyt *c*) from mitochondria. The release of Cyt *c* from mitochondria results in apoptosome formation, followed by the activation of procaspase-9, which in turn cleaves downstream effector caspases (Korsmeyer et al., 2000). Type II CD95 signaling might be blocked by Bcl-2 family members such as Bcl-2 and Bcl-x_L (Willis et al., 2003). Signaling downstream of TRAILR1/R2 receptors is similar to CD95 signaling.

TNFR, DR3 and DR6 signaling

TNF-R1 signaling differs from CD95-receptor or TRAILR1/R2-induced apoptosis (Varfolomeev and Ashkenazi, 2004). TNFR1 stimulation is postulated to result in the formation of two signaling complexes (Micheau and Tschopp, 2003). Complex I – formed at the membrane – comprises TNFR1, TNF, RIP (receptor-interacting protein), TRADD (TNFR-associated death domain protein), TRAF-1/2 (TNFR-associated factor), and probably other, as-yet-unidentified molecules. It is proposed to trigger the NF-κB signaling pathway through recruitment of the IKK complex and activates JNK through a TRAF-2-dependent mechanism. Complex I lacks FADD and procaspase-8 but is reported to translocate to the cytosol, where FADD, procaspase-8/10 and $FLIP_{L/S}$ are recruited to form the so-called traddosome or complex II (Micheau and Tschopp, 2003). Activation of procaspase-8 takes place in the traddosome and is followed by activation of downstream death signaling. In this model, the choice between survival and death depends upon the efficiency of complex II formation, caspase-8 activation and the amount of FLIP in the cells that blocks procaspase-8 activation at complex II. Although this proposed model provides an elegant mechanism of life-death decision making, it needs further experimental confirmation.

The DR3 and DR6 signaling pathways are less well characterized (Bhardwaj and Aggarwal, 2003). RIP and TRADD are recruited to the receptor complex, and DR3 and DR6 promote activation of NF-κB that leads to the expression of survival genes (Bhardwaj and Aggarwal, 2003; Karin and Lin, 2002).

Modulation of Death Receptor signaling

There are several levels of modulation of DR signaling (French and Tschopp, 2003). As mentioned above, decoy receptors can compete with DRs for ligand binding, and FLIP blocks procaspase-8 activation at the DISC. Further downstream, IAPs (inhibitors of apoptosis) inhibit effector caspase activation. Our current understanding of DR signaling has opened possibilities for the design of new therapeutic strategies for targeting death receptor pathways. This would allow the treatment of a number of diseases potentially associated with defects in DR signaling, such as multiple sclerosis and Alzheimer's disease.

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