Apoptosis in the Regulation of Immune Responses

MICHAEL J. PINKOSKI and DOUGLAS R. GREEN

ABSTRACT. Apoptosis, or programmed cell death, is an active process required for the regulation of immune responses. T cell apoptosis may represent a protective mechanism that limits peripheral damage by T cells during immune response. The underlying biological processes responsible for morphological aspects of apoptosis are becoming better defined. Concepts reviewed here include caspase activation, death pathways, and crosstalk between death ligands and their receptors. (J Rheumatol 2005;32 Suppl 74:19-25)

Key Indexing Terms:
APOPTOSIS
CASPASES
TUMOR NECROSIS FACTOR
IMMUNE RESPONSE

Apoptosis, or programmed cell death, is an active process required for the regulation of immune responses. Generation of a mature lymphocyte pool requires removal of autoreactive thymocytes and selection of a population sufficiently diverse to establish a comprehensively responsive peripheral lymphocyte repertoire. Peripheral lymphocytes undergo expansion in response to antigenic stimulation and must be capable of inducing apoptosis in target cells in order to resolve the offending infection. They must also acquire susceptibility to apoptotic stimuli that govern their removal in order to return to prestimulus numbers following resolution of the immune response to restore homeostasis.

Apoptosis was originally defined by morphological features[1,2], which are arguably still the most consistent defining features of this variety of cell death. Overall cell shrinkage, nuclear condensation, and chromatin margination are among the most recognizable of these. Blebbing of membrane-bound bodies known as apoptotic bodies is also clearly recognizable. The underlying biochemical processes responsible for the morphological aspects of apoptosis are becoming better defined, although not as clearly as most review articles on the subject would lead us to believe.

Apoptotic cell death is coordinated in cells by caspase proteases. Caspases are a family of cysteinyl-proteinases that have substrate specificity for cleavage at the C-terminal side of aspartate residues (see review[3]). Although not required for most forms of apoptosis, caspases coordinate the process[4]. They give a dying cell the appearance of apoptotic death, but in many cases, death will proceed even in the absence of active caspases[5].

From the perspective of activation, caspases can be divided conveniently into 2 groups: initiator and executioner. Each functional group is characterized by the molecular distinction of a long or short prodomain, respectively. The clue to caspase-activation requirements also correlates with the nature of the respective prodomains[3]. The prodomain contains an oligomerization/recruitment domain that determines the mechanism by which an inactive zymogen is converted into an active protease. The initiator caspases have long prodomains and are activated by oligomerization, whereas the executioner caspases have shorter prodomains and are activated by proteolytic cleavage events that allow proper folding of the active site.

Apoptosis is coordinated by a set of caspases called the executioner caspases. In humans these are caspase-3 and caspase-7. The only known way we can activate an executioner caspase is by sequential cleavage at 2 critical sites. There is one notable exception: another set of caspases. Caspase is the only protease identified capable of productively cleaving an executioner caspase. A further exception is granzyme B, a serine proteinase expressed by cytotoxic lymphocytes, including natural killer cells and cytotoxic T lymphocytes[6,7]. Once cleaved and properly folded, an executioner caspase will, in turn, cleave certain key enzymes in a doomed cell, which results in the phenomenon of apoptosis. For example, pro-caspase-3 (p32) is first cleaved by caspase-8 or granzyme B to yield p20 and p12 fragments, followed by autocatalytic processing to yield a mature p17 fragment, which is the α subunit that combines with the p12 (β-subunit) to form an active $(\alpha\beta)_2$ mature enzyme[8-10]. The second cleavage event is not required to generate an active protease in vitro and it has been proposed to play a role in activation in vivo[3].

Almost all caspases undergo a cleavage event concurrently with activation. In some cases, cleavage is required for protease activity (as with the executioner caspases), but this has led to the unfortunate misconception that the

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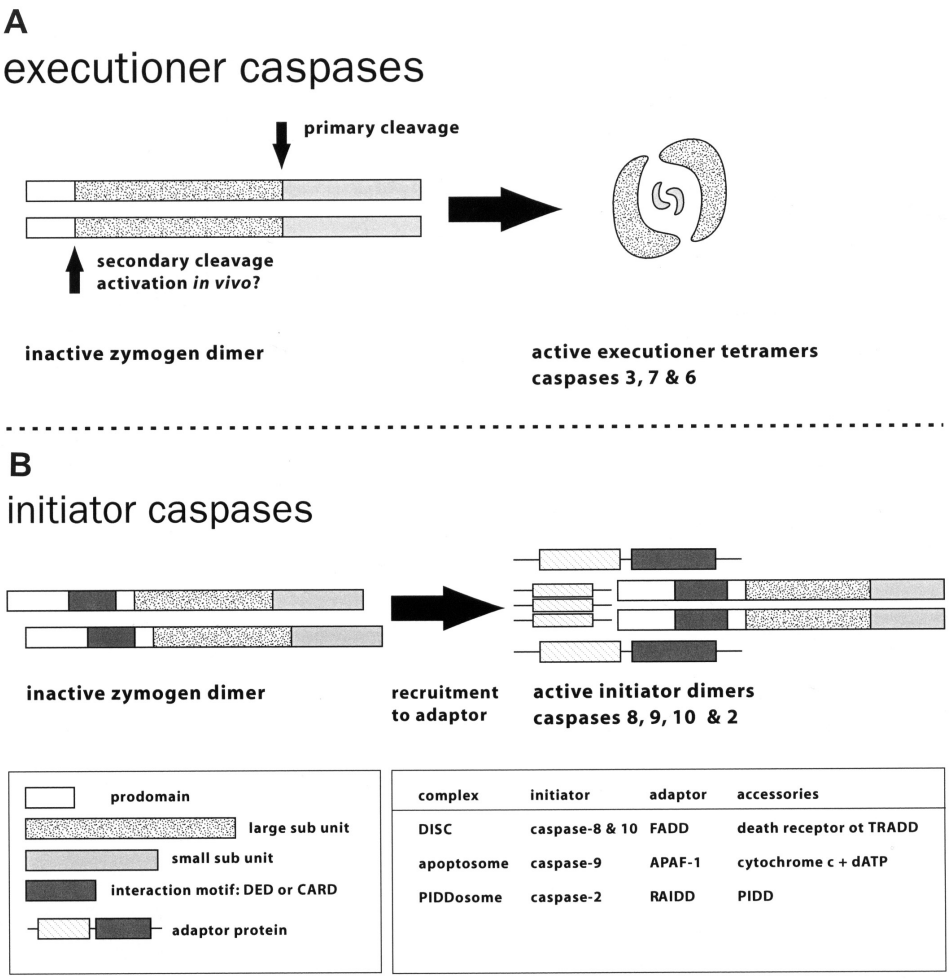

Figure 1. Caspase activation. A. Activation of the executioner caspases. These caspases have short prodomains that lack the death effector domain (DED) or caspase activation and recruitment domain (CARD) motif. Generation of an active enzyme requires proteolytic cleavage between the large and small subunits, 2 dimers of which form an ($\alpha\beta$)2 tetramer. Caspases-3 and -7 (and presumably caspase-6) exist as inactive dimers. Proteolytic cleavage between the large and small subunits is required to generate a proper fold resulting in a functional, active site. Removal of the prodomain may be required for activation *in vivo*. B. The initiator caspases-8, -10, -9, and -2 have long prodomains that contain DED or CARD motifs, which mediate the intermolecular interactions necessary to form complexes with their respective adaptors[38]. Activation of initiator caspases does not require proteolytic processing, but rather proximity. Proximity of 2 full length caspase-8 molecules can be induced by oligomerization of the death receptor Fas; in turn, Fas binds the death domain adaptor FADD, which binds pro-caspase-8, resulting in formation of an enzymatically active caspase-8 complex. Cleavage of caspase-8 may serve to stabilize the active complex. *In vitro* dimerization of pro-caspase-8 as a result of increased concentration can lead to the formation of an enzymatically active complex.

appearance of cleavage of products indicates an active caspase, or conversely, that a caspase is not active if there are no detectable cleavage products. While the executioner caspases are activated in this manner (Figure 1), it is certainly not the case for the initiator caspases. Caspases 8, 9, 10, and 2 have been shown to become enzymatically active by dimerization[3,11]. In the case of caspase-8 and caspase-9 (and now apparently caspase-2 as well) this is facilitated by interaction with an adaptor protein as part of a macromolecular complex. For caspase-9 the adaptor is APAF-1 in the apoptosome, along with cytochrome c and dATP; caspase-8 and caspase-10 interact with FADD (FAS associated death domain) as part of the DISC (death inducing signaling complex) and caspase-2 is complexed with RAIDD (RIP1 associated ICH1/CED3-homologous protein with death domain).

Obviously, if cleavage is not required for activation, then one cannot draw conclusions about activation (or lack of it) by Western blot analysis of probands. The initiator caspases, which possess long prodomains, are activated when brought into sufficient proximity to form a (dimeric) caspase, often in the context of additional adaptor molecules.

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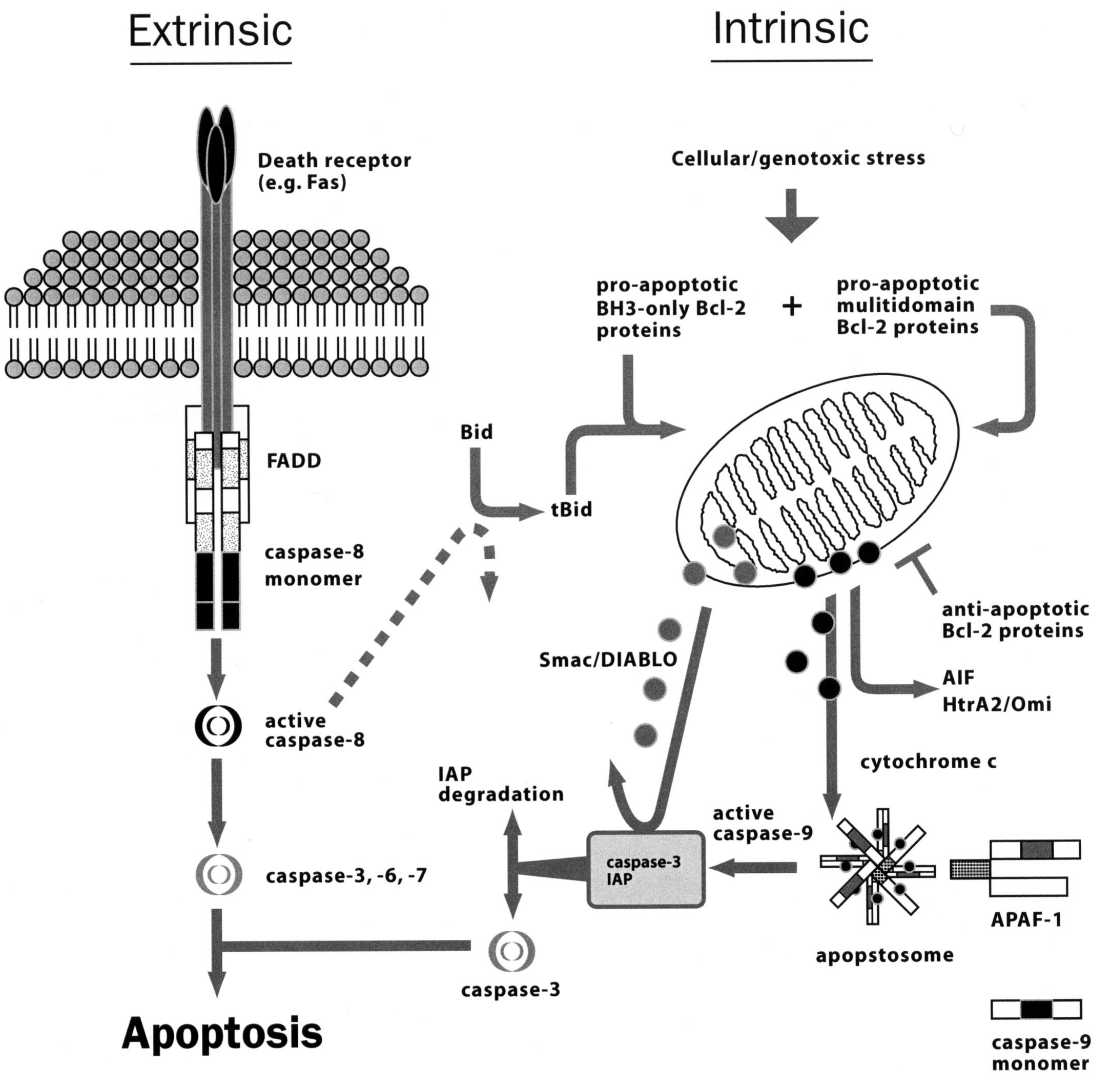

Figure 2. Extrinsic and intrinsic death pathways. The extrinsic pathway depicted on the left is characterized by the death-inducing signaling complex involving the Fas death receptor. Encountering its ligand (Fas-ligand, CD95L), Fas recruits the adaptor protein FADD via homotypic interactions between death domains of FADD and similar domains on the cytosolic portion of Fas. Pro-caspase-8 monomers interact with FADD via homotypic interactions between complementary death effector domain in FADD and the N-terminal prodomain of caspase-8. There are significant differences in the signaling complex initiated by engagement of TNF-R1. Engagement of TNF-R1 by TNF results in recruitment of TRADD, then FADD. Recent evidence suggests that the complex containing pro-caspase-8 dissociates from the membrane-bound complex. The cytosolic complex is then responsible for generation of active caspase-8, but the downstream effects appear to be similar. The intrinsic pathway is initiated by disruption or triggering of some intracellular process such as genotoxic stress, heat shock, or cytotoxic insult. This pathway relies on pro-apoptotic BH-3-only members of the Bcl-2 protein family in conjunction with pro-apoptotic multidomain family members (i.e., Bax, Bak, and Bok), which trigger release of mitochondrial proteins. Caspase-9 is the initiator caspase in this pathway. The apoptosome is activated by the release of cytochrome c from mitochondria and its subsequent association with APAF-1 and dATP, allowing recruitment of pro-caspase-9 to the complex. Pro-caspase-3, in turn, is recruited to the apoptosome and cleaved by caspase-9. Although enzymatically active at this point, caspase-3 is not yet capable of carrying out its apoptotic functions because it is bound by a member of the IAP family. Relief of inhibition by XIAP is facilitated by Smac/DIABLO, which is released from mitochondria coincidentally with cytochrome c. IAP: inhibitor of apoptosis protein; APAF-1: apoptotic protease-activating factor-1; AIF: apoptosis-inducing factor.

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Subsequent cleavage can and often does occur and appears to stabilize an active enzyme prior to degradation.

The effective unit of active caspase-8 is a dimer[11]. Forced dimerization results in productive protease activity. There are 2 major types of substrates for caspase-8 and each determines whether death will occur via the intrinsic or extrinsic pathway (discussed below). Direct activation of executioner caspases (caspase-3 or -7) can occur only if there are no further inhibitions to overcome. Cleavage and activation of Bid, a pro-apoptotic member of the Bcl-2 protein family[12,13], engages the mitochondrial death pathway, which ultimately results in activation of the executioner caspases, but utilizes caspase-9, another initiator caspase[14].

Although there are numerous stimuli to induce apoptosis, each fits into one of 2 categories: the intrinsic and extrinsic pathways (oversimplified in Figure 2; see also[15]). The extrinsic pathway is induced by engagement of one of the death receptor members of the tumor necrosis factor (TNF) receptor superfamily by their corresponding death ligands. Caspase-8 (or perhaps -10) acts as the initiator caspase and is capable of directly activating the executioner caspases. The intrinsic pathway is initiated by triggering an intracellular process by such events as genotoxic stress, heat shock, or cytotoxic insult[16]. The intrinsic pathway relies on pro-apoptotic BH-3-only members of the Bcl-2 protein family in conjunction with pro-apoptotic multidomain family members (i.e., Bax, Bak, and Bok) that trigger release of mitochondrial proteins[17]. This pathway is inhibitable by the prosurvival members of the Bcl-2 family. The intrinsic pathway utilizes caspase-9 as the initiator caspase.

For most forms of apoptosis the activation of the executioner caspase is through so-called initiator caspases. In the intrinsic mitochondrial pathway of apoptosis the initiator caspase is caspase-9, which is activated in a macromolecular complex known as the apoptosome. The apoptosome is activated by the release of cytochrome c from mitochondria[14,18] and its subsequent association with APAF-1, dATP, and procaspase-9[19]. In this situation caspase-9 serves as the initiator caspase, and its activation is dependent on the release of cytochrome c from the mitochondria. Procaspase-3 is recruited to the apoptosome and is cleaved by caspase-9. Although enzymatically active at this point, caspase-3 is not yet capable of carrying out its apoptotic functions because it is bound by a member of the IAP (inhibitor of apoptosis protein) family, primarily XIAP. Relief of inhibition by XIAP is facilitated by Smac/DIABLO[20-22], which is released from mitochondria coincidentally with cytochrome c, but perhaps not in a mechanistically or temporally identical fashion.

Figure 2 outlines the agents involved in death receptor-induced apopotosis. This is the picture shown in virtually every review article on TNF receptor function for induction of apoptosis. This model, although simplified, appears to be an adequate representation of Fas-mediated death, but recent evidence suggests that this is not the case with respect to TNF-R1 signaling to death. Until a year ago this was the only model we had for how death receptors triggered caspases. However, it is almost certainly not how TNF receptor activates caspase-8 to induce death. Evidence suggests that this is more complicated.

FADD, the adaptor model that engages caspase-8, does not bind the TNF-R1 intracellular region (for review see[23]). This function is served by yet another adaptor molecule, TRADD (TNF receptor associated death domain), that binds ligand-bound TNF-R1. It was assumed that TRADD binds TNF-R1 and then recruits FADD to form a big complex on the receptor. However nobody has been able to precipitate a complex involving TNF-R1, TRADD, and FADD. Recently, Tschopp proposed a completely different model based on solid evidence[24]. Tschopp's group proposes that when TNF-R1 is bound by ligand, it recruits TRADD. It is not yet clear what the stoichiometry is, but we suspect that the receptor pre-exists as a trimer. The evidence for the pre-existing Fas trimer is very good, but there is only correlative information for TNF-R1. TNF-R1 likely exists as a trimer and when TRADD is recruited to the intracellular region of TNF-R1, TRADD undergoes some sort of modification, as yet undetermined. TRADD changes molecular weight, possibly due to phosphorylation, and dissociates from the receptor. Biochemical evidence suggests that TRADD dissociates in a dimeric form capable of recruiting FADD, which in turn recruits and activates caspase-8 within the cytosol.

This represents a fundamentally different mechanism for death receptor function. For a long time we thought all death receptors recruit and activate caspase-8 at the plasma membrane, but the suggestion is that in TNF-R1-mediated apoptosis signaling, the caspase is activated in the cytosol by a modified cytosolic adaptor molecule.

CROSSTALK BETWEEN MEMBERS OF THE DEATH RECEPTOR/LIGAND FAMILY

In the case of TNF-R1, there are 2 principal consequences of receptor engagement: one leading to apoptosis in a manner similar to that mediated by Fas, and the other involving induction of a number of genes leading to survival. The survival (or at least non-apoptotic) signal that comes from the TNF receptor proceeds by activation of nuclear factor-B (NF-κB)[25]. It has been demonstrated that the induction of NF-κB through the TNF receptor inhibits TNF induced apoptosis. That said, we still do not have a solid mechanism whereby activation of NF-κB inhibits the apoptotic process. We do know that it involves the expression of some key genes, but there are many genes, and no single gene is responsible for inhibiting NF-κB and inhibiting TNF-induced apoptosis (see[25]).

The involvement of NF-κB in TNF-R1 signaling is well established. RelA knockout mice, which show severe-

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ly limited ability to activate NF-κB through the TNF receptor, die *in utero* because TNF destroys the liver[26,27]. If these mice are crossed to mice lacking TNF-α (TNF-α–/–) or TNF receptor (TNF-R1–/–), they survive to birth and live for a short time[28,29]. However, they do poorly without TNF receptors or NF-κB because their inflammatory responses are completely absent.

NONLYMPHOID TISSUES IN PERIPHERAL DELETION

Immune privilege is a condition in which certain tissues allow for minimal, if any, infiltration by peripheral lymphocytes[30,31]. Cells in tissues such as the eye, testes, and ovaries constitutively express Fas-ligand, which appears to provide a defensive barrier by killing Fas-bearing lymphocytes. This limits infiltration before onset of a potentially devastating inflammatory response. Certain tissues such as the intestinal epithelium, liver, and lung do not constitutively express Fas-ligand, but rather, they upregulate Fas-ligand in response to infiltrating lymphocytes[32-34]. Induced expression of Fas-ligand is proposed to limit the extent of lymphocyte infiltration tolerated within these tissues[35]. In fact, expression of Fas-ligand by non-lymphoid tissues is required to provide optimal deletion of peripheral lymphocytes following expansion triggered by either superantigen or peptide antigen[34].

Surprisingly, a key mediator of Fas-ligand induction in intestinal epithelial cells (IEC) was found to be TNF-α[33]. IEC constitutively express TNF-R1 and induce Fas-ligand expression in response to TNF-α *in vitro* and *in vivo*.

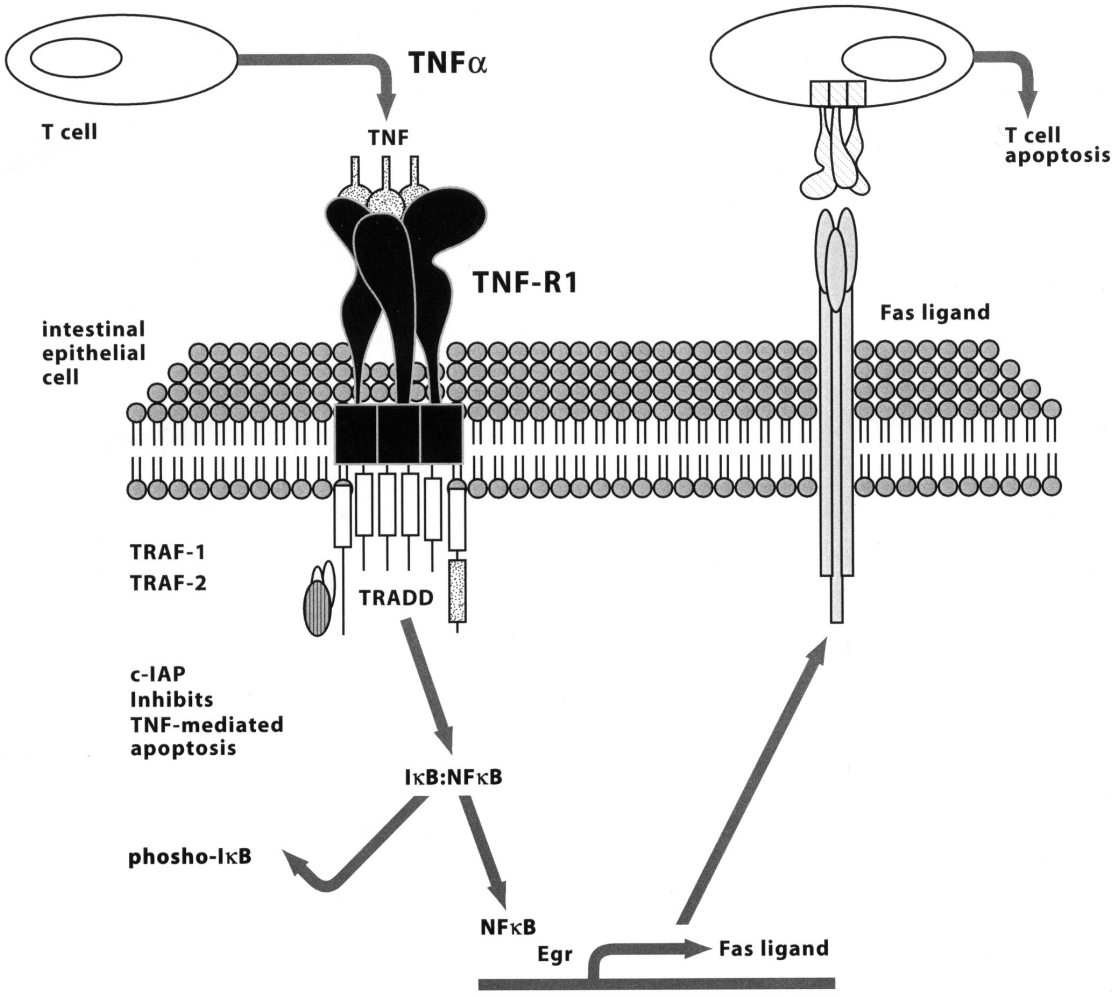

Figure 3. Crosstalk between death ligands and receptors. Activated T cells, which produce TNF-α, percolate through the small intestine. This signal is detected by the intestinal epithelial cells, which constitutively express TNF-R1 (p55). Rather than leading to death, TNF-R1 signaling results in the induction of Fas-ligand expression by a mechanism involving NF-κB activation and members of the Egr family of transcription factors. Intestinal epithelial cell Fas-ligand is capable of inducing apoptosis in Fas-bearing cells, including activated T cells. This model is an example of inducible immune privilege proposed to contribute to limiting the extent of infiltration by activated T cells into certain peripheral tissues. TRAF: TNF receptor associated factor; c-IAP: inhibitor of apoptosis protein.

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Although a direct connection has yet to be demonstrated unequivocally *in vivo*, TNF-α is produced by activated lymphocytes. Also, activated lymphocytes and IEC TNF-R1 or exogenous TNF-α and IEC TNF-R1 are required to induce Fas-ligand promoter activity. Prevention of NF-κB activation by use of a non-phosphorylatable superrepressor IκBαM abrogates the ability of TNF-α to induce Fas-ligand expression. The principal regulation of Fas-ligand in this context is governed by responsive elements in the proximal promoter, notably those for NF-κB and the Egr family of transcription factors[33,36].

At this point it seems a reasonable to ask why the intestinal epithelium would respond to TNF-α, a potentially lethal and otherwise inflammatory cytokine, by inducing another death ligand. Our data suggest that this is a sensing mechanism allowing certain tissues to accommodate a limited lymphocyte infiltration without eliciting consequences from a disseminated inflammatory response[37]. Activated lymphocytes, which traffic along the epithelium of the small intestine, produce TNF-α. The IEC, sensing the presence of activated lymphocytes, upregulate Fas-ligand, possibly in conjunction with other anti-apoptotic proteins, which results in triggering of apoptosis in Fas-bearing lymphocytes (Figure 3).

In the intestinal epithelium, the induction of Fas-ligand is greatest at the base of the crypt and extends diminishingly up the length of the villi[32,34]. This corresponds with the appearance of activated lymphocytes that percolate through the small intestine. Real-time polymerase chain reaction analyses show that that injection of T cells with appropriate antigen causes strong expression of Fas-ligand mRNA in purified intestinal epithelial cells[33,34,36]. Expression of IEC Fas-ligand is very transient and coincides with the expansion and deletion of peripheral lymphocytes following antigenic challenge[37]. This is presumably due to the reduction of TNF-α levels as the infiltrate is managed; it ensures that IEC Fas-ligand expression is in a microenvironment limited to the sites of infiltration. As a corollary of this model, sustained TNF-α levels, and hence sustained Fas-ligand expression, lead to the killing of additional Fas-bearing cells, including those of the endothelium, which in turn could lead to a more widespread inflammation. The similarity between Fas-ligand expression in immune privilege and that induced in nonlymphoid tissues in response to lymphocytes led us to propose the descriptive term for this phenomenon: "inducible immune privilege."

The implications of inducible Fas-ligand expression by nonlymphoid tissues is observed by transferring and tracking lymphocytes from T cell receptor transgenic animals in recipient animals that are either wild type or defective for Fas-ligand[34]. After immunization these animals display lymphocyte expansion in response to antigen. Consistent with our original experiments using superantigens[32] we observed the same lymphocyte proliferation in response to antigen in the presence or absence of Fas-ligand in the periphery[34]. If Fas-ligand is present in the peripheral nonlymphoid tissue, there is a dramatic deletion of the activated lymphocytes. However, in the absence of nonlymphoid Fas-ligand there is a significant enhancement in the survival of the cells over time, which can be extended until one month. Thus the epithelial cells express Fas-ligand; moreover, fas-ligand is expressed at the same site where T cells go. When an animal is injected with T cells and then immunized, the T cells percolate through the tissue in the same regions that are expressing Fas-ligand in the intestinal epithelial cells.

Where does TNF-α fit in all this? The stimulation of T cells in these animals induces Fas-ligand expression, but the intestinal epithelial cells also express TRAIL and TNF in response to the same stimulation. Activated T cells induce death ligand expression in epithelial cells. Nonlymphoid Fas-ligand contributes to peripheral deletion and therefore it is possible that Fas ligand induced T cell apoptosis represents a protective mechanism that limits peripheral damage by T cells during immune responses. That said, it turns out that expression of TRAIL or Fas-ligand in the nonlymphoid cells of the small intestine is absolutely dependent on TNF-α production by the T cells. TNF-α knockout mice do not induce Fas-ligand in response to antigen-dependent lymphocyte expansion and deletion. Similarly, intestinal epithelial cells in TNF-R1 knockout mice do not respond to activated T cells *in vivo* with respect to the ability to induce expression of Fas-ligand.

What this has to do with autoimmunity is not yet clear. Our working model is based on a manageable inflammatory response (i.e., not full blown autoimmunity), caused by the lymphocytes that percolate into the tissue, and unless a certain threshold is exceeded, TNF-α produced by those lymphocytes will trigger the expression of death ligands in the surrounding tissue that feeds back and reduces the number of T cells in that tissue (see[35]). As a consequence, it is possible to temper the extent of peripheral immune responses; we therefore suggest this would also temper the potential for inflammatory damage. This working hypothesis has yet to be demonstrated rigorously in models of autoimmune inflammatory pathologies.

This model predicts that crosstalk between both TNF/TNF-R and Fas/Fas-ligand will be necessary to regulate the process *in vivo*. Potential damage could arise from infiltrating lymphocytes themselves (directly or indirectly) if they are not properly removed, or by Fas-ligand expressing IEC that fail to downregulate Fas-ligand and inappropriately induce apoptosis in other neighboring Fas-bearing cells.

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