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MINIREVIEW

FLICE-Inhibitory Proteins: Regulators of Death Receptor-Mediated Apoptosis

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Cell death is executed along several pathways. Apart from necrotic cell death occurring upon tissue injury, several distinct types of apoptosis have been observed. Apoptosis, or programmed cell death, is critical for tissue homeostasis in multicellular organisms. It plays an important role in many physiological processes, especially in development and in the immune system (39, 80). Many diseases are associated with either too much or too little apoptosis, such as AIDS, cancer, and autoimmunity (39).

On the molecular level, the cell death program can be divided into three parts: initiation, execution, and termination of apoptosis. Apoptosis is initiated by a variety of stimuli, including growth factor withdrawal ("death by neglect"), UV or γ-irradiation, chemotherapeutic drugs, and death receptor signals. In most cases the execution phase is characterized by membrane inversion and exposure of phosphatidylserine, blebbing (zeiosis), fragmentation of the nucleus, chromatin condensation, and DNA degradation. In the termination phase, "apoptotic bodies" are engulfed by phagocytes (39).

The growing subfamily of death receptors is part of the tumor necrosis factor (TNF)/nerve growth factor receptor superfamily. This superfamily is characterized by a sequence of two to five cysteine-rich extracellular repeats. The death receptors contain an intracellular death domain (DD), which is essential for transduction of the apoptotic signal. Six members of this subfamily are known so far, TNF-R1 (also called CD120a), CD95 (APO-1/Fas), DR3 (APO-3, LARD, TRAMP, and WSL1), TRAIL-R1 (APO-2 and DR4), TRAIL-R2 (DR5, KILLER, and TRICK2), and DR6 (67). Among these, CD95 is the best-characterized death receptor (65).

Death receptors are activated by their natural ligands, which have coevolved as a death ligand family, called the TNF family. Except for lymphotoxin α, the death ligands are type II transmembrane proteins which can be converted into a soluble form by the activity of metalloproteases. Several groups reported activity of the soluble CD95 ligand (CD95L) (38), whereas others ascribe the capacity to induce apoptosis to the membrane-bound form (66, 74). Recently, it has been proposed that the activity of soluble CD95L is enhanced by interaction with the extracellular matrix (4). The roles of soluble and membrane-bound CD95L remain to be shown in vivo.

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The salient point of death receptor signaling is the formation of a multimolecular complex of proteins triggered by receptor cross-linking either with agonistic antibodies (77) or with death ligands. The structure formed is called the death-inducing signaling complex (DISC) (see Fig. 2A) (36, 37, 71, 82). Among the death receptors, the CD95 DISC has been characterized most extensively. It consists of oligomerized, most probably trimerized, CD95, the serine-phosphorylated adapter Fas-associated death domain protein (FADD)/Mort 1, two isoforms of caspase 8 (caspase 8/a [FLICE, Mach-α1, and Mch5β] and caspase 8/b [Mach-α2]) (50), and CAP3 (a molecule that contains the N-terminal death effector domains [DED] of caspase 8 and an as yet uncharacterized C terminus) (36). According to recent findings, FADD and caspase 8 are also recruited to the DISC of TNF-related apoptosis-inducing ligand R1 (TRAIL-R1) and TRAIL-R2 (7, 37, 71) and are essential for death induction via TRAIL-R2 (71).

Caspases are a family of aspartate-specific cysteine proteases that are necessary for execution of apoptosis. Caspases are synthesized as proenzymes (zymogens) that are activated by proteolytic cleavage. The active enzyme is a heterotetrameric complex of two large subunits containing the active site and two small subunits. Activation of caspases has been reported to occur after a variety of apoptotic stimuli, including death receptor signals (13).

The stoichiometry of the DISC components is not clear, but the necessity of their interactions has been elucidated and lies in the nature of their corresponding subdomains. Oligomerization of CD95 creates a conformation of the receptor DD which, by homophilic interaction, binds the adapter FADD/Mort1 via its DD. In addition to a DD, FADD possesses an N-terminal DED with which it binds procaspase 8 and CAP3. Procaspase 8 is then cleaved at the DISC in three consecutive steps, which lead to the formation of active caspase 8, consisting of a heterotetramer of two p10 and two p18 subunits (see Fig. 2B). The prodomain of caspase 8 remains at the DISC, while active caspase 8 dissociates from the DISC to start the cascade of caspase activation which constitutes the execution phase of apoptosis (47).

Recently, it was reported that death receptors are assembled prior to triggering via so-called pre-ligand binding assembly domains (8, 69). In this case signaling would be induced either by conformational changes of preformed death receptor trimers or, alternatively, by formation of multimeric complexes upon ligand binding.

Several knockout and transgenic mice underscore the cen-

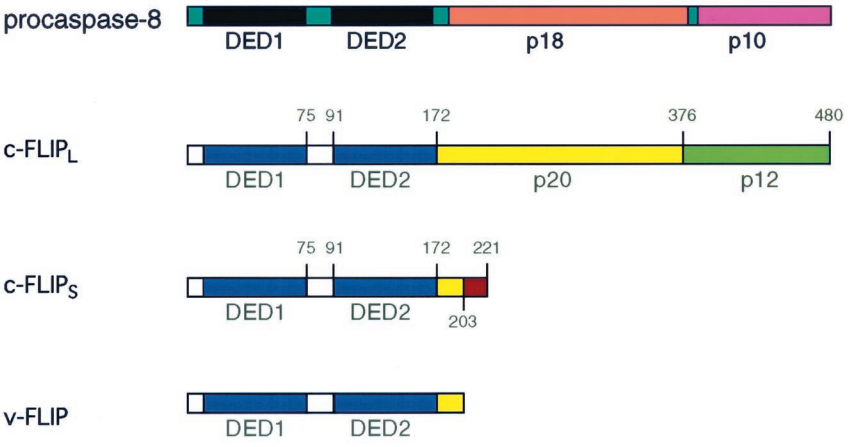

FIG. 1. Structural similarities between caspase 8 and FLIP. For details, refer to the text.

tral role of the DISC-associated molecules FADD and caspase 8 in signaling via death receptors (79, 88). FADD and caspase 8 knockout mice die at embryonic day 11. They show cardiac failure and abdominal hemorrhage. To study embryonic lethality, FADD$^{-/-}$ chimeric mice were constructed. In thymocytes of these mice, CD95-mediated apoptosis was completely blocked. The same applied to FADD$^{-/-}$ fibroblasts.

Death receptor-mediated apoptosis can be modulated at both the receptor level, e.g., by glycosylation (33, 56), and further downstream by interfering with the apoptotic signaling cascade. For example, inhibitor-of-apoptosis proteins directly inhibit caspases (for a review, see reference 11), and antiapoptotic members of the Bcl-2 family inhibit apoptosis of so-called CD95 type II cells, in which apoptosis is dependent on a mitochondrial pathway (62).

In this review, we discuss the role and mechanism of apoptosis modulation by FLICE-inhibitory proteins (FLIPs).

v-FLIPs

Database mining led to the identification of an entire family of DED-containing proteins (6, 25, 76). Some of these proteins are components of viruses of the gammaherpesvirus class, such as herpesvirus saimiri, human herpesvirus 8, a Kaposi's sarcoma-associated herpesvirus, and moluscum contagiosum virus. These proteins were called viral FLICE-inhibitory proteins (v-FLIPs) (76). v-FLIPs consist of two DEDs (Fig. 1). They were shown to bind to the CD95 DISC and thus inhibit activation of caspase 8. v-FLIPs were capable of inhibiting apoptosis induced via several death receptors (CD95, TNF-R1, DR3, and DR4), suggesting that these receptors use similar signaling pathways (48). In human herpesvirus 8, the v-FLIP coding region is represented by a bicistronic mRNA following the coding region of v-cyclin (19). These coding regions are separated by an internal ribosome entry site (44). v-FLIP is expressed at low levels in latently infected cells (44, 60, 73), but its expression is increased in late Kaposi's sarcoma lesions or upon serum withdrawal from lymphoma cells (44, 73). Deletion of the v-FLIP gene from the genome of herpesvirus saimiri confirmed the antiapoptotic effect of v-FLIP but revealed that it is not essential for replication, transformation, or pathogenicity of herpesvirus saimiri (16).

Mice carrying a T-cell-specific v-FLIP-E8 transgene show strongly reduced thymocyte numbers, although thymocytes of these mice are resistant to CD95-mediated apoptosis (53). The reduction in thymocyte numbers seems to be independent of the CD95 system, since it was also observed in a CD95$^{-/-}$ background. Interestingly, the thymic phenotype resembles that of T cells from FADD dominant-negative transgenic mice, suggesting that another death receptor system distinct from the CD95 system is critically involved in thymocyte selection (52, 84).

c-FLIPs

A human cellular homolog of v-FLIPs was found and termed cellular FLICE-inhibitory protein (c-FLIP; also called FLAME-1, I-FLICE, Casper, CASH, MRIT, CLARP, and usurpin) (17, 20, 26, 29, 30, 57, 68, 72). The c-FLIP gene is located on chromosome 2q33-34 in a cluster of 200 kb together with caspase 8 and caspase 10, suggesting that these genes evolved by duplication (57). Multiple splice variants of c-FLIP have been reported, but so far only two, designated c-FLIP$_S$ and c-FLIP$_L$, could be detected on the protein level (63).

c-FLIP$_L$ contains tandem DEDs and a caspase-like domain (Fig. 1). However, it lacks amino acid residues that are critical for caspase activity, most notably the cysteine of the catalytic center. c-FLIP$_S$ resembles its viral counterparts, only consisting of two DEDs and a short C-terminal part that differs from c-FLIP$_L$ (30).

Initially, both proapoptotic (17, 20, 29, 68) and antiapoptotic (17, 26, 30, 57, 72) effects were proposed. Enhanced cell death occurred mainly in experiments using transient overexpression and may have been due to excessive loads of DED-containing proteins that form death effector filaments (70). Data obtained from cells stably overexpressing c-FLIP and from mice deficient in c-FLIP clearly support an antiapoptotic function (30, 32, 41, 57, 63, 87)

MECHANISM OF ACTION

Conflicting data exist about the direct interaction partners of c-FLIP. Among them are FADD (17, 30, 68, 72), caspase-3 (20, 68), caspase 8 (20, 26, 30, 57, 68, 72), caspase 10 (17, 26, 72),

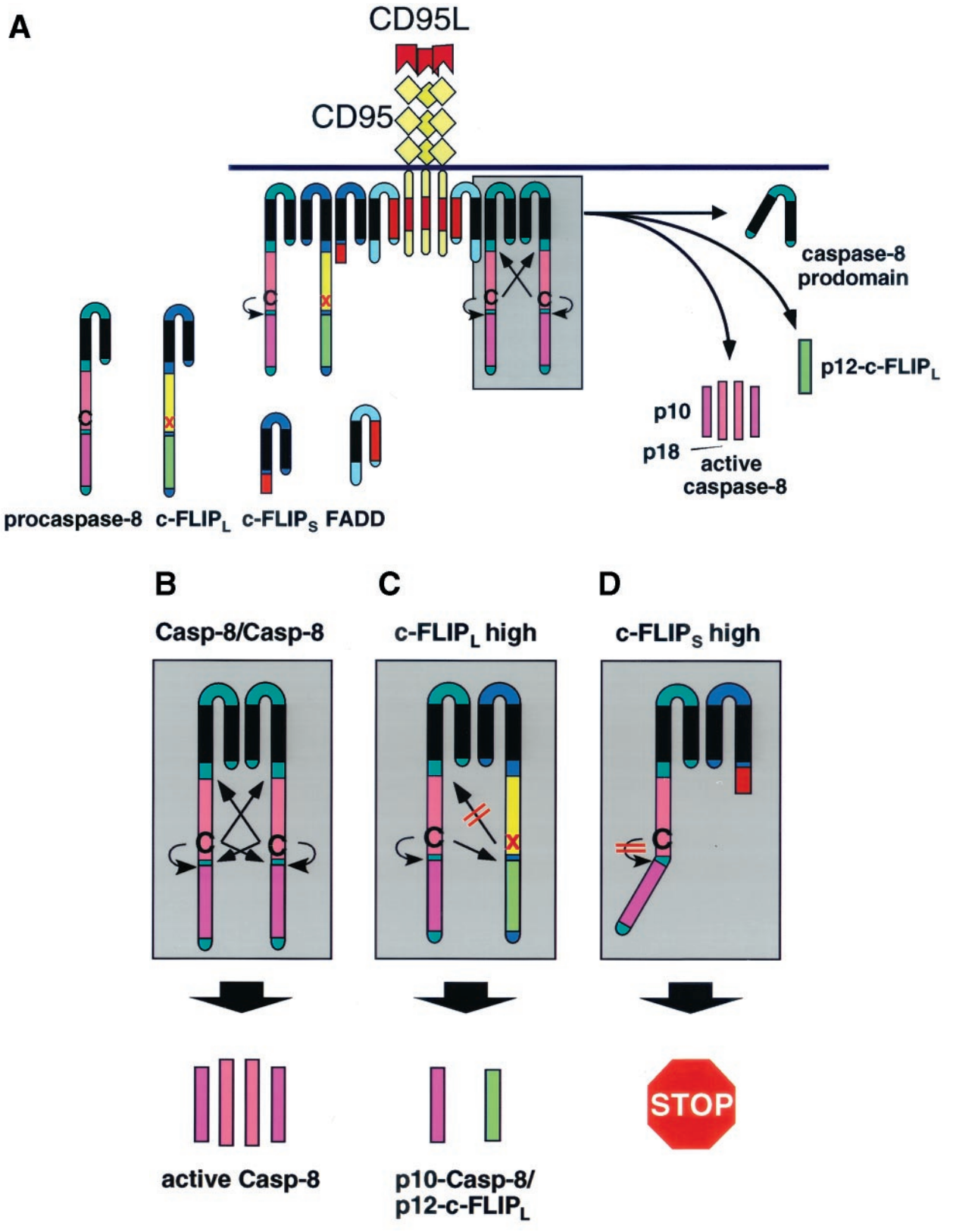

FIG. 2. Model for c-FLIP-mediated inhibition of procaspase 8 processing at the DISC. (A) The CD95 DISC. For details, refer to the text. (B to D) Depending on the ratio of procaspase 8 and c-FLIP proteins at the DISC (A, grey box), different products are released from the DISC upon receptor triggering. (B) Small amounts of c-FLIP proteins allow processing of procaspase 8, leading to the formation of the active caspase 8 heterotetramer composed of the p18 and p10 subunits. (C) In the presence of large amounts of c-FLIP$_L$ procaspase 8 is recruited into the DISC, and cleavage is blocked after generation of the p43 cleavage products of both caspase 8 and c-FLIP$_L$. (D) In the presence of large amounts of c-FLIP$_S$ procaspase 8 is recruited into the DISC but remains unprocessed. In each case, modulation of caspase 8 cleavage renders cells resistant to CD95-mediated cell death.

TRAF1 (68), TRAF2 (68), and Bcl-x_L (20). However, it was also reported that c-FLIP does not interact with FADD (26, 29, 63) or caspase 8 (63) prior to triggering of death receptors.

The mechanism of cell death attenuation by c-FLIP has not been completely elucidated. It was suggested that c-FLIP, as a potential competitive inhibitor, precludes recruitment of caspase 8 to the DISC and thereby prevents its activation (57). This idea was supported by the fact that upon overexpression of the viral homolog v-FLIP-E8, it was recruited to the DISC, thereby interfering with caspase 8 recruitment and activation (76).

Scaffidi et al. demonstrated that the cellular FLIP proteins c-$FLIP_S$ and c-$FLIP_L$ are also recruited to the DISC. However, this does not preclude caspase 8 from recruitment to the DISC (63). It could be shown that c-$FLIP_L$ is cleaved into a p43 subunit that remains at the DISC and a p12 subunit which is released. In the presence of c-$FLIP_L$ caspase 8 is still cleaved upon recruitment to the DISC (Fig. 2C) (63). However, its cleavage is incomplete, leading to the generation of the p43 and p41 subunits and concomitant release of the p10 subunit (41). Recently, we were able to show that large amounts of c-$FLIP_S$ completely prevent caspase 8 processing at the DISC (Fig. 2D) (41). Assuming that caspase 8 processing at the DISC occurs via trans- and autocatalytic cleavage of dimers according to the induced-proximity model (51), these results suggest that the initial step of caspase 8 cleavage proceeds autocatalytically, but requires a caspase domain as a counterpart in order to achieve an active conformation. This caspase domain can even be inactive, as in the case of c-$FLIP_L$. In contrast, the second step of caspase 8 processing occurs transcatalytically and therefore requires functional caspase 8 as a counterpart of the dimer. These results explain the fact that in the presence of c-$FLIP_S$ procaspase 8 is not cleaved at all. However, it remains to be clarified in detail whether the differences in the mechanisms of apoptosis inhibition also reflect different functional roles of c-$FLIP_S$ and c-$FLIP_L$ and by which downstream mechanisms they are mediated.

REGULATION OF C-FLIP EXPRESSION

The signaling pathways by which c-FLIP expression is modulated are not well understood. It was reported that mitogen-activated protein (MAP) kinase kinase 1 (MKK1) was able to rescue concanavalin A-stimulated Jurkat cells from CD95-induced apoptosis, which correlated with an increase in c-FLIP mRNA expression (86). Moreover, inhibition of MAP kinase activity led to decreased c-FLIP expression on the transcriptional level. Upregulation of c-FLIP induced by transforming growth factor beta (TGF-β) in microglia was also reported to be blocked by inhibition of MAP kinases (64). However, modulation of c-FLIP levels was not observed upon CD3 triggering of Jurkat cells, although apoptosis could be augmented by inhibition of MAP kinases (23). It was suggested that MAP kinases rather modulate phosphorylation of the proapoptotic Bcl-2 family member Bad than influence the DISC. Recently, it was demonstrated that within a panel of tumor cell lines, only in a certain subset was c-FLIP expression dependent on MAP kinases (54). In contrast, c-FLIP expression seemed to be dependent on the activity of the phosphatidylinositol 3-kinase/Akt pathway in all cells tested. Thus, the contribution of kinase signaling pathways to modulation of c-FLIP remains elusive and might be cell type dependent. Two recent studies showed that c-FLIP is upregulated upon activation of NF-κB (40, 49).

Metabolic inhibitors acting on either transcription or translation were shown to rapidly abolish c-FLIP expression, indicating that c-FLIP mRNA is unstable (15). Modulation of mRNA stability has been shown to be a potent mechanism of regulating protein levels in other systems (24). It might well be that modulation of c-FLIP expression is achieved similarly.

PHYSIOLOGICAL ROLES FOR C-FLIP

A number of potential physiological stimuli responsible for c-FLIP-mediated rescue from death receptor-induced apoptosis have been suggested. In this respect the immune system has been at the center of investigation.

One of the initial studies described the downregulation of c-$FLIP_L$ in activated primary T cells, suggesting that downregulation of c-FLIP renders T cells susceptible to activation-induced cell death (AICD) (30). Moreover, it was reported that interleukin-2 (IL-2) enhances AICD in $CD4^+$ T cells by upregulation of CD95L and concomitant downregulation of c-FLIP mRNA (59). Downregulation of c-FLIP upon IL-2 administration was later linked to the G_1/S transition of activated T cells because T cells treated with cell cycle-blocking reagents do not downregulate c-FLIP (3). Retrovirus-mediated reconstitution of c-FLIP in activated murine T and B cells rescued these cells from CD95-mediated AICD (78).

In vivo, increased c-FLIP expression led to the production of autoantibodies and to the development of autoimmune diseases, suggesting that modulation of c-FLIP is necessary in order to maintain self-tolerance (78). In contrast to the studies described above, Scaffidi et al. did not detect any modulation of c-FLIP proteins upon stimulation of primary human T cells (63). Instead, the transition from resistance to sensitivity correlated with an increase in the capacity to form a DISC despite comparable amounts of CD95 surface expression. Thus, freshly activated T cells resemble CD95 type II cells, whereas long-term activated T cells resemble type I cells. In parallel, T cells switch from a Bcl-x_L-high to a Bcl-x_L-low state, allowing apoptotic activation of mitochondria. Since DISC formation itself is affected in this switch, it seems unlikely that c-FLIP plays a major role in rendering T cells sensitive to AICD. Until now, there has been no conclusive explanation for the differences observed. However, one might speculate that species differences between humans and mice have to be faced here.

So far, most of the studies concerning c-FLIP have focused on the long form, c-$FLIP_L$, most likely because it is generally more abundant in cells. However, c-$FLIP_S$ was recently identified as a new effector of CD28-mediated costimulation (35) and as a mediator of resistance to AICD after T-cell receptor (TCR) restimulation (34). CD28 costimulatory signals led to protection from anti-CD3-triggered apoptosis by interfering at three different levels in the signaling cascade: (i) by prevention of upregulation of CD95L, (ii) at the mitochondria by induction of Bcl-x_L, and (iii) at the DISC by upregulation of c-$FLIP_S$. This last level of protection might prove to be the most important one because it prevents cells not only from suicide, but also from fratricide, and is far more upstream in the apoptotic signaling cascade than Bcl-x_L. Restimulation of activated

primary human T cells via the TCR also led to massive upregulation of c-FLIP$_S$, which prevented DISC activity after triggering of the CD95 pathway and therefore protected from apoptosis. An upregulation of murine c-FLIP upon repeated antigen exposure was also observed in a TCR-transgenic model (28). Repeated stimulation by antigen leads to the generation of memory T cells (42, 45). Therefore, upregulation of c-FLIP$_S$ levels might be one of the molecular mechanisms that determines T-cell memory.

The homeostasis not only of T cells but also of B cells seems to involve modulation of c-FLIP$_L$ levels. Recently, it was reported that c-FLIP$_L$ is upregulated and recruited to the DISC in human tonsillar B cells upon ligation of CD40 or the B-cell receptor for antigen (BCR) (21, 85). Moreover, c-FLIP$_L$ seems to be part of the regulatory mechanism that determines survival of germinal center B cells after successful affinity maturation of the BCR (22). Upon receipt of the survival signal via CD40, c-FLIP$_L$ persists at the CD95 DISC and thus protects germinal center B cells from undergoing apoptosis.

Dendritic cells (DCs) and macrophages form another important part of the immune system, being responsible for antigen presentation to T and B cells, but also for a number of autoimmune diseases like rheumatoid arthritis and atherosclerosis. Macrophages differentiate from circulating blood monocytes and thereby switch from a CD95-sensitive to a CD95-resistant phenotype, which correlates with increased expression of c-FLIP (55). Immature DCs capture antigen in peripheral tissues and deliver it to lymphoid organs. During migration, the DCs mature, i.e., they reduce their capacity to capture antigen and increase expression of costimulatory molecules. After 2 days, mature DCs disappear from lymphoid organs, presumably by undergoing apoptosis. Recently, it was reported that immature but not mature DCs are susceptible to death receptor-mediated apoptosis, whereas mature but not immature DCs highly express c-FLIP$_L$ (43). Therefore, the disappearance of mature DCs from the lymphoid organs seems to be independent of the death receptor system, which might be more important to maintain homeostasis of immature DCs.

c-FLIP is prominently expressed in cardiac tissue. It has been reported that in infarcted cardiac tissue, c-FLIP expression is reduced (57). Cardiac myocytes that underwent apoptosis upon ischemia and reperfusion lacked c-FLIP expression, in contrast to surrounding healthy tissue. Interestingly, mice deficient in c-FLIP die at embryonic day 10.5 most probably due to cardiac failure (87). These results suggest that c-FLIP plays an essential role in heart development. The cardiac phenotype of c-FLIP$^{-/-}$ mice strongly resembled that of caspase 8$^{-/-}$ and FADD$^{-/-}$ mice (79, 88). These similarities suggest that for heart development, a functional interplay between the three DISC components FADD, caspase 8, and c-FLIP is absolutely required. However, the question arises whether this interplay requires a signal from a known or unknown death receptor or a different type of receptor. Moreover, it remains elusive whether the signal required for heart development is associated with regulation of apoptosis or opens up a novel role for the three molecules involved. Since the phenotypes of the three types of deficient mice are similar, although c-FLIP is antiapoptotic whereas FADD and caspase 8 are proapoptotic, it is very suggestive that apoptosis-independent signaling defects give rise to the hemorrhagic phenotype. However, assuming that apoptosis needs to be tightly regulated for tissue formation during embryonic development, dysregulation of apoptosis might still be the cause of hemorrhagic failure.

It has also been reported that anoikis (matrix detachment) (5) and apoptosis of endothelial cells induced by oxidized low-density lipoprotein (LDL) (61) correlated with modulations of c-FLIP expression.

Dysregulation of apoptosis signaling is often associated with disease formation. Alterations in sensitivity and resistance to death receptor-mediated apoptosis have been reported to be involved in autoimmune diseases (38) and cancer (14). As described above, c-FLIP is an important regulator of these apoptosis signaling pathways and might therefore account for the development of such diseases. In human melanoma cells, the expression level of c-FLIP correlated with resistance to TRAIL-induced apoptosis (18). However, this correlation was questioned after analysis of a broader panel of melanoma cell lines (89). Recently, it was reported that in Epstein-Barr virus (EBV)-transformed cells, resistance to CD95-mediated apoptosis correlated with an increased c-FLIP/caspase 8 ratio (75). Therefore, high levels of c-FLIP might contribute to EBV-induced tumorigenesis in Burkitt's lymphoma.

It has also been reported that both v-FLIP and c-FLIP mediate the immune escape of tumors (12, 46). Tumors with high expression levels of c-FLIP were shown to escape from T-cell-mediated immunity in vivo, although the perforin-granzyme pathway was not impaired. In addition, it was demonstrated that in vivo tumor cells were selected for elevated c-FLIP levels (46). v-FLIP promoted tumor establishment and progression in vivo by prevention of death receptor-mediated cytotoxicity (12).

As described above, there is a broad line of evidence for c-FLIP's being one of the central regulators of death receptor-mediated apoptosis. However, it should be kept in mind that both function and potential physiological roles of c-FLIP have been controversial, e.g., the role of c-FLIP in AICD of T cells and in melanoma cells. It is important to mention that at present it is not clear what amounts of c-FLIP are required to protect cells from apoptosis or whether it is the concentration of c-FLIP or the ratio between c-FLIP and caspase 8 or CD95 that determines sensitivity or resistance. Most reports on the involvement of c-FLIP in regulation of physiological processes are based on correlations that still wait for substantiation by careful mechanistic analysis or interference with c-FLIP expression. Therefore, mice with tissue-restricted deficiency of c-FLIP would give the deepest insight into its physiological role.

TRANSCRIPTIONAL ACTIVATION THROUGH c-FLIP

One of the death receptors, TNF-R1, has a dual role and transmits both death signals, similar to CD95, and survival signals via activation of NF-κB (83). CD95 is generally described as a pure death receptor. However, several studies suggest that proliferative signals also emanate from CD95 (1, 2, 58). Recently, it was reported that c-FLIP enhances the proliferative signaling pathway of CD95 after TCR triggering in Jurkat cells by increased recruitment of RIP, TRAF1, and TRAF2 to the CD95 DISC, which then leads to activation of

NF-κB and ERK signaling pathways (31). Similar observations have been made in mice transgenic for human c-FLIP$_L$ (31).

The modulation of NF-κB signaling pathways was also demonstrated for other viral and human DED-containing proteins, such as several v-FLIP proteins, FADD, caspase 8, and caspase 10 (9, 10, 27). For c-FLIP, caspase 8, and caspase 10 the activating effect was assigned to the tandem DED. Furthermore, it was shown that caspase activity was dispensable for activation of NF-κB. In contrast to the studies described above, Wajant et al. showed that NF-κB activation upon death receptor triggering is dependent on a factor that is sensitive to metabolic inhibitors (81). They reported that overexpression of c-FLIP or a deficiency in FADD inhibited signaling to NF-κB. Finally, it is important to mention that NF-κB activation was not altered in c-FLIP$^{-/-}$ mice (87). Thus, the role of c-FLIP and its homologs and the role of death receptors as such in activation of proliferation signals require further investigation, especially with respect to in vivo conditions.

CONCLUSIONS

Signaling via the CD95 system has been under intense investigation in recent years, and considerable progress has been made in the elucidation of death induction (for a review, see reference 65). However, regulation of the death receptor systems is not well understood yet.

The c-FLIP proteins seem to be major players in modulation of the death signal. This statement is likely to hold despite a number of controversies. Several physiological and pathological conditions were proposed to be dependent on blocking of apoptosis by c-FLIP. However, it has to be kept in mind that regulatory processes are often complex, and thus, correlation of expression levels with biological effects is often not convincing. In addition, the question of the functional difference between the two splice variants of c-FLIP remains. So far, they have proved to be comparably efficient in inhibiting death receptor-mediated apoptosis (30) but seem to interfere at different levels (41). With respect to NF-κB activation, no major differences have been observed (31). Finally, the existence of more than the two splice variants on the protein level remains to be shown.

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