FLIP ing the coin? Death receptor-mediated signals during skin tumorigenesis

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Accepted for publication 28 February 2008

Abstract: Keratinocyte skin cancer is a multi-step process, during which a number of obstacles have to be overcome by the tumor cell to allow the development of a manifest tumor. Beside proliferation and immortality, apoptosis resistance is one additional and critical step during skin carcinogenesis. Over the past two decades, much has been learned about the prototypical membrane-bound inducers of apoptosis, namely the death receptors and their ligands, and the apoptosis signalling pathways activated by death receptors have been elucidated in great detail. In contrast, much less is known about the tissue-specific role of the death receptor/ligands systems during the development of skin cancer. Here, we summarize and discuss the role of this intriguing receptor family and the potential mechanistical impact of the intracellular caspase-8 inhibitor cFLIP for keratinocyte skin cancer. Given more recent data about cFLIP and its isoforms, a more complex regulatory role of cFLIP can be suspected. Indeed, cFLIP may not solely interfere with death receptor-mediated apoptosis signalling pathways, but may positively or negatively influence other, potential harmful signalling pathways such as the production of inflammatory cytokines, tumor cell migration or the activation of transcription factors such as NF-κB, considered crucial during skin tumorigenesis. In this respect, cFLIP may act to 'FLIP the coin' during the development of keratinocyte skin cancer.

Key words: anoikis – apoptosis – cFLIP – death receptors – skin cancer

Please cite this paper as: FLIP ing the coin? Death receptor-mediated signals during skin tumorigenesis. Experimental Dermatology 2008; 17: 614–622.

Skin cancer and death receptors: defining the play ground

Skin cancer is a complex multistep process that requires several genetic alterations of keratinocytes. Ultraviolet (UV) B irradiation represents the widely accepted major carcinogen that causes distinct genetic aberrations excellently reviewed elsewhere (1,2). Supplementary genetic or epigenetic events for tumor development may be tumor stroma-initiated changes induced by the tumor or the host itself (3). These pathological and pathophysiological factors ultimately disturb the integrity of molecules involved in crucial cellular processes like proliferation, survival and programmed cell death (apoptosis). Such alterations of the tumor cells and their surrounding stroma impact the cellular homeostasis ultimately leading to a manifest (and potentially metastatic) keratinocyte-derived skin tumor. In this context, the role of apoptosis resistance has been clearly established as one important necessity for tumor development (4). Several forms of cell death have been defined based upon biochemical, morphological and functional properties (5). Apoptosis is generally considered as inherent ability of single cells within multicellular organisms to undergo self-induced death, facilitating the efficient removal of superfluous or genetically damaged cells. Apoptosis is induced by both physiological (e.g. hormones and growth factors) and harmful stimuli (e.g. UV irradiation or infections) (5). Importantly, apoptosis is distinct from necrosis (usually accompanied by substantial inflammation of the surrounding tissue and early loss of plasma membrane integrity) or autophagic cell death (6).

Conceptually, the cellular program of apoptosis has been divided by its activation mode in either ‘intrinsic’ or ‘extrinsic’ signalling pathways. The intrinsic pathway is largely activated in response to cellular stress conditions, serum starvation or cytotoxic drugs. Although the precise triggering mechanisms are still poorly understood, the Bcl-2 family of proteins controls the intrinsic cell death pathway. The Bcl-2 proteins are divided into subgroups of molecules with anti-apoptotic (e.g. Bcl-2, Bcl-XL, Bcl-w, A1, Mcl-1 and BOO) and proapoptotic function (‘BH3-only’ proteins like Bim, Bid, Bmf, Noxa, Puma and Hrk; and the
subgroup of BAX/BAK like proteins). The BAX/BAK subgroup (containing BAX, BAK, BOK and Bcl-Xs) are kept inactive by anti-apoptotic Bcl-2 proteins. These, in turn, are inactivated by ‘BH3-only’ proteins like Bim, Bid, Bmf, Bik, Noxa and Puma. The BH3-only proteins are regarded as decisive sensors of cellular stress regulating the intrinsic cell death pathway (7–9). These events regulate the release of proapoptotic proteins from the intermembranous space of mitochondria, namely cytochrome c, endonuclease G, AIF and Smac/DIABLO (10). Once released from mitochondria, these proteins activate a downstream cascade of cysteine proteases, known as the caspases (11,12). In the mitochondrial pathway of apoptosis, the initiator caspase-9 is crucial for the activation of the effector caspases, the executioners of the apoptotic cell death program (11). These caspases finally cleave a multitude of cellular substrate proteins, thereby irreversibly resulting in apoptotic cell death (13). The massive proteolytic activity exerted by caspases leads to the characteristic apoptotic phenotype of the dying cell.

The so-called extrinsic cell death pathway utilizes death receptor (DR) interaction with their respective ligands to trigger apoptosis. To date eight different DR have been described, including TNF-R1, CD95, TRAIL-R1, TRAIL-R2, DR3, DR6, EDAR and NGFR (14). Specific aspects of the signalling pathways utilized by the different DR have been broadly summarized previously (15–17). While many details about the signalling capabilities of these receptors have been elucidated, their physiological function in different organ systems remains unsolved, despite the fact that these receptors are widely expressed (14). Altogether, protection from DR-mediated apoptosis has been proposed as one important step in the development of malignancy, enabling tumor cells not only to survive and escape anti-tumor immune responses, but also to develop resistance to chemotherapy (18). Therefore, conceptually, molecules that block DR-mediated signals may act as oncogenes, while proteins augmenting DR-mediated apoptosis could be viewed as tumor suppressors.

The players of the game: DR-associated proapoptotic proteins

How does DR signal for their presumed major function, the induction of apoptosis? DR consists of an extracellular region that contains several cysteine rich domains essential for ligand binding and a transmembrane domain to anchor the DR at the cell surface. The cytoplasmic region called the death domain (DD) that couples DR to the caspase cascade represents the defining structural element of the receptor family. Engagement of DR with their ligands results in receptor trimerization and clustering of the DD which in turn facilitates the recruitment of the adaptor proteins Fas-associated death domain-containing protein (FADD) or TNFR1-associated death domain (TRADD) (19). FADD enables the recruitment of the proform of the initiator caspase-8 to the DR and leads to formation of a multimolecular signalling platform known as the death-inducing signalling complex (DISC). The formation of the DISC allows the dimerization of procaspase-8 molecules that stimulates their proteolytic activity, cleavage and release of active caspase-8 molecules into the cytosol (20). The active enzyme initiates apoptosis in DR-sensitive cells by cleaving substrates such as Bid, a pro-apoptotic member of the Bcl-2 family, or caspase-3. The indispensable role of the adaptor molecules for DR-mediated apoptosis have been highlighted in a number of in vitro models that associated the deficit or low levels of FADD, caspase-8 or caspase-3 with resistance to DR-induced apoptosis and, consequently, the evolution of malignancy (19).

Each step in DR-mediated apoptosis is tightly regulated to avoid the inappropriate self-destruction of the cell under physiological conditions. Indeed, multiple regulatory events have been discovered that modulate the response of cells to DR ligation. First, the expression level of a particular DR or the expression of so-called ‘decoy receptors’, namely TRAIL-R3, TRAIL-R4, DcR3 and osteoprotegerin may determine the sensitivity of a cell for the respective death-inducing ligands. Although mostly obtained under overexpressing conditions, these closely related receptors lack a functional intracellular DD. Differential expression of these receptors may alter the subcellular localization of receptor complexes within the cell, as shown for TRAIL-R3 and TRAIL-R4 (21) rather than simply acting as ‘decoy’ for ligand binding. In addition, the DR expression on the cellular surface is regulated in a highly cell-type specific manner at the post-translational level via largely unknown mechanism (22). The second important mechanism that regulates the response to DR ligation is the internalization of DRs following their stimulation. More recent data indicate that this is a crucial step for the outcome of receptor triggering (23,24). Another aspect, relevant in the pathophysiological context of carcinogenesis is the notion that mutations or gene polymorphisms of DR (exemplified by TRAIL-R1) have been described, potentially interfering with its apoptotic function. Interestingly, a subset of squamous cell carcinoma cells carries mutations in the DD that led to DR apoptosis resistance (25). An additional level of complexity is added by the fact that epigenetic silencing by DNA methylation interferes with important proapoptotic molecules such as TRAIL-R1 in the absence of mutations, as recently reported (26). Lastly, the cellular environment may impact the DR systems: interferons (α and γ) are able to increase the sensitivity to DR-mediated apoptosis and – as major effector molecules expressed during T-cell activation – may thereby critically influence death receptor
sensitivity in the skin during the intricate interplay between keratinocytes and skin-infiltrating T cells (27). This might either depend on increased death receptor expression, as shown for CD95 in response to IFNγ (28–30) or by modification of the dynamics of caspase activation at the DISC (31). Taken together the data from a large number of in vitro studies, an inflammatory cytokine milieu may result in sensitization of formerly resistant cells to the proapoptotic action of death ligands. In the context of tumor development, this sensitization may preclude invasion of tumor cells in the surrounding stroma. Thus, tumor progression may require upregulation of anti-apoptotic molecules or, conversely, loss of proapoptotic proteins. Intriguingly, a shift in the balance between these pro- and anti-apoptotic proteins may lastly be sufficient to avoid tumor progression by apoptosis induction or conversely promote tumor progression at the interface between tumor and surrounding stroma (32).

One of the referees: cFLIP as apical inhibitor of DR signalling

Given the potential danger of unwanted apoptosis and the ubiquitous expression of DR, it is not surprising that naturally occurring intracellular anti-apoptotic proteins exist that can block different stages of the apoptotic cascade, most importantly at two different levels: inhibitors of effector caspases, in particular inhibitor-of-apoptosis proteins (IAPs) (33,34), or molecules able to block initiator caspase activation, as exemplified by the inhibitor cellular Flice-inhibitory protein (cFLIP) [for review see (35,36)]. cFLIP inhibits one of the most proximal steps of DR-mediated apoptosis. Two isoforms of cFLIP are commonly detected in human cells: a long form (cFLIPL) and a short form (cFLIPS). cFLIPL, a 55 kDa protein, contains two DED and a caspase-like domain, while cFLIPS, a 26 kDa protein, closely resembles its viral counterparts, consisting only of two DED (37). The structure of cFLIPL resembles that of procaspase-8 but lacks its active proteolytic center within the caspase-like domain. Thus cFLIP proteins could at the first glance be considered intrinsic dominant-negative inhibitors that keep caspase-8 in check. Both isoforms are recruited to the DISC, form heterodimers with procaspase-8, prevent its activation and in turn block DR-mediated apoptosis. cFLIP is crucial to DRs such as CD95 and TRAIL-R, but appears less critical to TNF-R1-mediated death in keratinocytes (38). Intriguingly, the mechanism of action differs for distinct cFLIP isoforms: while cFLIPα completely blocks caspase-8 cleavage by preventing the initial cleavage step of procaspase-8, cFLIPL allows this initial processing to a p43 fragment but inhibits the final cleavage step that prevents the release of active caspase-8 into the cytosol where its substrates reside (39,40). Surprisingly, cFLIPL does not interfere with enzymatic activity within the DISC, but rather interferes with the release of active caspase-8 from the DISC (41,42), thereby suggesting a more complex picture for the physiological role of cFLIP proteins beyond apoptosis protection.

Is it possible that the apoptosis inhibitor cFLIP might also regulate other DR-mediated signals? It could be hypothesized that such signalling events, in turn, may be important for tumor-promoting functions such as proliferation, migration, inflammation or metastasis. Indeed, while all DR are able to initiate proapoptotic signals, it is now accepted that TNF-R1, DR3, TRAIL-R1/TRAIL-R2 or CD95 also transmit such signals to the DR-expressing cell. Activation of the transcription factor NF-κB, activation of the PKB/Akt pathway and mitogen-activated protein kinases (MAPK) such as cJun n-terminal kinase (JNK), ERK and p38 have been demonstrated to be a consequence of DR triggering [for review see (20)]. Of interest, there is now a large body of evidence that these DR-induced additional (non-apoptotic) signals are not necessarily needed to modulate apoptosis induction but rather initiate various other cellular responses. For example, activation of MAPK as well as NF-κB signalling pathways have been reported by death receptors (via CD95 and TRAIL-R) in the skin (43,44). These functions may have important and distinct stage-specific pathophysiological consequences during different stages of skin tumorigenesis (compare Fig. 1).

Decisions to be taken by the referee: cFLIP, death receptors and their relation to other critical signalling pathways of skin tumorigenesis

How does the complicated regulation of DR signalling pathways relate to the process of skin tumorigenesis? It is long known that the acquisition of mutations of the tumor suppressor protein p53 is a critical and early event during tumorigenesis of the skin (45), and the invasion of the epidermal stem cell niche is required for further expansion of the initial patches of p53-mutated keratinocytes (2). Interestingly, partial loss of wild-type p53, as experimentally obtained by a stable siRNA expression, results in an apoptosis-susceptible population of keratinocytes rapidly eliminated by UV irradiation in vitro (46). UV irradiation, however, is known to induce several death ligands such as TNF and CD95L that are involved in the process of UV-induced apoptosis (28,47). Moreover, DR clustering was shown to contribute to UV-induced apoptosis (48,49). Taken together, it is tempting to speculate that loss of part of p53’s function may lead to an apoptosis sensitive population of keratinocytes within the epidermis. These transformed keratinocytes might be eliminated by the first squad of host resistance mechanism, namely one or several
Death ligands. These death ligands may either be expressed or induced by keratinocytes, or could be produced by immune cells or the tumor stroma. Therefore, during this early stage of skin carcinogenesis, initiated transformed keratinocytes might be particularly susceptible to specific induction of apoptosis by UV irradiation or direct contact to death ligand expressing cells from, for example, cytotoxic T cells (compare Fig. 1). Support for such a concept comes from earlier in vitro and in vivo work: loss of CD95L allows the earlier acquisition of p53 mutations in mouse skin, indicative of a tumor suppressive role of CD95L (50). A different death receptor is crucial during skin carcinogenesis in the mouse: the loss of TNF-R1 leads to increased numbers of papillomas and invasive squamous cell carcinomas whenever the activity of NF-κB is blocked, indicative that TNF-R1 might be essential for the elimination of early transformed cells (51). NF-κB, in turn, inhibits skin carcinogenesis in human keratinocytes based upon data that demonstrated that an inhibitor of NF-κB promotes skin tumorigenesis. Recent data have highlighted the role of TNF-R1-dependent skin-intrinsic JNK activation for this tumor-promoting function (52–54). Thus, although we lack comprehensive data about the role of distinct death receptors in the context of skin tumorigenesis, at least some of the death receptors (e.g. TNF-R1, CD95) signals are most certainly crucial for early steps of tumorigenesis of the skin. In this context, TNF-R1 as well as CD95L have to be considered as tumor suppressors. In addition, more recent data indicate that the murine TRAIL-DR is a metastasis suppressor, while primary tumor development was unaffected in a murine model of skin cancer (55). Interestingly, the sole murine TRAIL-DR was crucial to mediate DR-mediated cell death upon detachment (in general called anoikis). Anoikis is known to be a critical mechanism to prevent early metastasis in human keratinocytes. Keratinocyte anoikis utilizes a caspase-8-dependent pathway and keratinocyte stem cell survival appears to depend upon survivin expression (56–58). Interestingly, cFLIP confers anoikis resistance in keratinocytes and other cell types (57,59) and anoikis induced by the compound anisomycin requires a blockade of cFLIP protein synthesis (58). Conversely, although most certainly cell-type specific, the loss of the proapoptotic caspase-8 was critical for metastasis development in neuroblastoma, supporting a concept of caspase-8-dependent signalling pathways as suppressor of metastasis (60). In this context, cFLIP as potent caspase-8 inhibitor may represent a central regulator to block the inhibitory function of caspase-8 for metastasis, thereby formally representing a metastasis promoter. Future studies are necessary to clarify this hypothesis.
Taken together, the hypothesis that cFLIP not only interferes with apoptosis or anoikis signalling pathways directly, but may also deviate DR-mediated apoptotic or other signalling pathways of the cell into potentially deleterious proliferative or progression-promoting metastatic signals appears of relevance during tumor progression. The fact that different death receptors might be important during distinct stages of skin carcinogenesis highlight the complex role of death receptor-mediated signals during this process and place cFLIP at the center stage of this process. Based upon the data about distinct functions of death receptors in the process of skin carcinogenesis, it is surprising that the role of proximal adaptor molecules has not been studied more intensively. Such studies for skin carcinogenesis, in particular for cFLIP and caspase-8, have been hampered by the lethal phenotype of the respective knockout mouse models (61,62). Therefore, these questions await further study in conditional skin knockout mice (63,64). Intriguingly, the role of other death receptors remains obscure at the time of writing this article, but will most likely reveal more about the complex interplay between death receptors and their ligands during skin carcinogenesis.

What is known about death receptors and their ligands in human tumor samples that might well show significant differences when compared with mouse models? When examined in actinic keratosis as well as squamous cell carcinoma (SCC) of the skin, both tumor stages express CD95, while CD95L expression is increased in SCC as compared with actinic keratosis (65). Moreover, cFLIP expression is lost in actinic keratosis, while its expression is increased in progressed SCC (66). Although it has been assumed that the major effect of defective CD95 signalling may be the resistance of UV-irradiated keratinocytes to UV-induced apoptosis, there is evidence that death receptor family members such as CD95L or TRAIL activate non-apoptotic signalling pathways and thereby may actively influence the outcome of death receptor triggering in the skin, in particular under conditions when apoptosis induction is prevented, as exemplified by cFLIP (42–44,67,68). Interestingly, TRAIL-R expression is unaltered during tumor progression of mucosal SCC and does not influence primary skin tumor formation (55,69). However, the ligand may act in a non-apoptotic fashion whenever apoptosis induction is blocked at the intracellular level (Fig. 1). For example, if TRAIL-induced apoptosis in highly sensitive human transformed keratinocytes is blocked by cFLIP, this change in composition of the DISC results in efficient blockade of NF-κB. This indicates that cFLIP blocks this DR-mediated proinflammatory signal (42). In contrast, activation of the MAPK ERK is not altered by high levels of cFLIP, suggesting that death receptors might signal for proliferation under certain conditions (70,71). In turn, an increased sensitivity of transformed keratinocytes by either intrinsic genetic, epigenetic or paracrine mechanisms (such as IFNs) may have a protective role at certain tumor stages and may thus preclude further progression (Fig. 1). However, it is currently unknown if cFLIP is regulated by IFNs. Future studies in this direction will elucidate, which scenario holds true in vivo in humans, and should include broader methodology such as proteomics to allow the integrative analysis of a multitude of different signalling pathways that may crosstalk with death receptor apoptosis signalling pathways. Nonetheless, the current knowledge highlights the complexity of regulatory events involved in the process of UVB-induced carcinogenesis and its interplay with DR-mediated signals and suggest that cFLIP may indeed represent an important ‘referee in the game’ of skin carcinogenesis.

**Tackling the goal: cFLIP as a potential therapeutic target in skin cancer**

Could cFLIP represent a potential target for therapeutic efforts in skin cancer? The experimental evidence lined out above is indeed not only relevant for the interaction between cytotoxic T lymphocyte (CTL) and tumor cells (generally accepted as a concept of ‘tumor surveillance’), but also for the development of resistance to chemotherapeutic agents. Therefore, tumor cells may evade CTL immune responses or chemotherapeutic treatment through the acquisition of resistance to DR-mediated apoptosis, and cFLIP may represent one important candidate molecule in this context. Indeed, using siRNA-mediated regulation of endogenous cFLIP, reduction of cFLIP increased sensitivity to DR-mediated apoptosis in a multitude of experimental systems (40,72–74). In line, upregulation of cFLIP expression is frequently observed in melanoma (40,75,76), while much less is known about the role of cFLIP in keratinocyte-derived skin tumors in vivo. It will be interesting to study the effect of cFLIP modulation in different progression stages of skin tumors in the future to test the outlined hypothesis more directly. However, in vitro studies have clearly shown that cFLIP expression correlates with resistance to DR-induced apoptosis in the skin (42,77). Furthermore, in other models of malignancy, it was demonstrated that tumors expressing higher levels of cFLIP are more aggressive in vivo (78) and that cFLIP protects against T-cell mediated cytotoxic immune responses in vivo (78,79). In accordance with these findings, specific downregulation of cFLIP using antisense oligonucleotides or small interfering RNAs sensitize cells to death ligand-induced apoptosis in vitro (38,40,73), and cFLIP levels were inversely correlated with sensitivity to TRAIL in keratinocytes (77). In turn, death ligands might be activated by other tumor-specific signals generated during interference with oncogene-activated signalling
pathways, as has been shown in basal cell carcinomas (80). It has to be kept in mind that beside genetic aberrations of genes, epigenetic modulations of cFLIP might well be relevant during tumorigenesis. cFLIP itself has been shown to be a highly regulated molecule with a short half-life within most cells [(36,77); compare Fig. 2]. First, cFLIP itself is a transcriptional target of NF-κB that, in turn, is activated by several death receptors including TNF-R1. Furthermore, several important post-transcriptional mechanisms are operative for the regulation of cFLIP and may thus be tackled by compounds known to block these respective signaling pathways and that are currently developed or already used for tumor therapy: First, translation initiation, in particular for cFLIPS, is mediated by mammalian target of rapamycin (mTOR) (81). Second, cFLIP L is regulated by the JNK-activated ubiquitin ligase ITCH that targets cFLIP for proteasomal degradation (82). Lastly, several post-translational modifications of cFLIP L, in particular caspase-8-mediated (and remarkably DISC-independent) cleavage to a p22 fragment activate NF-κB by interaction of cFLIP p22 with NF-κB essential modulator (NEMO) and FADD. This DISC-independent event may be crucial for inflammatory responses, but may well have growth-inhibitory effects based upon the previous carcinogenesis data for keratinocytes (83). Thus, it could be hypothesized that cFLIP may also have DISC-independent functions in the skin. Intriguingly, cFLIP L, but not cFLIPS, is a potent activator of the Wnt signaling pathway (84), and could be important during skin carcinogenesis in a DR-independent as well as DR-dependent manner (85). Taken together, targeting cFLIP expression as tumor treatment might be achieved using mTOR inhibitors that block cFLIP translation. Proteasome inhibitors able to interfere with the NF-κB pathway that induces cFLIP transcription may as well interfere with cFLIP expression. Other compounds known to sensitize cells to DR-mediated apoptosis by downregulation of cFLIP protein may also prove to be clinically useful. These substances include compounds such as 4-(4-chloro-2-methylphenoxy)-N-Hydroxybutanamide), also known as 5809354, the synthetic triptenoid 2-cyano-3,12-dioxoolean-1,9-bien-28-oic acid (CDDO) or histone deacetylase inhibitors such as suberoylanilide hydroxamic acid. Last but not least, siRNAs targeting cFLIP might either restore sensitivity to endogenous death ligands or allow sensitization to TRAIL-R agonists currently in clinical trials [compare Fig. 2; (86)].

It has to be kept in mind that the body’s own death ligand production seems to be involved in keeping tumors...
at bay. This fact appears particularly relevant, when apoptosis via death receptors is not blocked by molecules such as cFLIP. Taken together, cFLIP represents a central regulator between apoptotic and non-apoptotic signals exerted by the DR family, and may ‘FLIP the coin’ to decide the fate of DR-triggered cells in the epidermis: cFLIP is thus at the center stage, whenever DR triggering may either lead to elimination by DR-mediated apoptosis or rather activate signals like proliferation, migration, inflammation or tumor progression. These signals may be of paramount importance for cellular activation and could as well be mandatory for the formation of a permissive stroma required for tumor progression of keratinocyte skin cancer. Although we have learned a huge number of details about signalling capabilities and their consequences for the death receptors, there might be many more surprises in the future of skin cancer research with respect to these initially pure anti-apoptotic molecules. Understanding these pathways in greater detail will allow us to assess if therapeutic strategies aiming at the specific regulation of anti-apoptotic inhibitors such as cFLIP may be successful and allow a better treatment of advanced or metastatic skin cancer.

Acknowledgements

This article is dedicated to Dr. Barbara A. Gilchrest in recognition of her help, encouragement and continuous support over the years. M.L. is supported by grants of the Wilhelm-Sander-Stiftung (2000.092.2) and Deutsche Krebshilfe (106849).

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