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Understanding the Role of the Death Receptor 5/FADD/caspase-8 Death Signaling in Cancer Metastasis

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Abstract

The normal function of the extrinsic apoptotic pathway is to mediate apoptosis. Thus, this pathway is generally recognized to be critical in host immune surveillance against cancer. However, many studies have suggested that some key components in this pathway including Fas, death receptor 5 (DR5), Fas-associated death domain (FADD) and caspase-8 may contribute to cancer growth or metastasis. Our recent study on DR5 and caspase-8 expression in human head and neck cancer tissues indicate that high caspase-8 either alone or along with high DR5 in tumor tissue from patients with lymph node metastasis is significantly associated with poor disease-free survival and overall survival, suggesting that these proteins may be involved in positive regulation of cancer metastasis. Thus, efforts should be made to better understand the role of the death receptor 5/FADD/caspase-8 death signaling in regulation of cancer metastasis.

Keywords

Caspase 8; DR5; FADD; Fas; Metastasis

The extrinsic death receptor-mediated apoptotic pathway is known to be critical in host immune surveillance against cancer. Intriguingly, increasing number of studies suggest that this death signaling pathway may also exert non-apoptotic function in enhancing cancer growth or metastasis. Our recent study on detection of DR5 and caspase-8 in human head and neck squamous cell carcinoma (HNSCC) supports this notion as well (1). This article will briefly review current research-related to this topic in the literature and discuss our findings in HNSCC.

Death Receptor 5 (DR5)/FADD/caspase-8 Signaling

DR5, like other death receptors, is activated by binding to its ligand, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and initiates apoptosis through interaction with the adaptor protein, Fas-associated death domain (FADD), which further recruits and activates caspase-8 (2, 3). The cellular FLICE-like inhibitory protein (c- FLIP), a truncated and dominant-negative homologue of caspase 8, inhibits the activation of the DR5-mediated death signaling by competing with caspase-8 for binding to FADD (4, 5). Thus, the DR5/FADD/caspase-8 signaling normally mediates an important apoptotic pathway (i.e., extrinsic apoptotic pathway).

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Conflicts of Interest
No potential conflicts of interest to disclose.

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Cancer Metastasis and Apoptosis

Cancer-related deaths occur largely due to the development of uncontrolled metastases. Thus the major reductions in cancer-related deaths will require effective strategy to prevent or eliminate disease dissemination (6). Metastasis is an inefficient process involving multistep events, in which only a small proportion of the many cells that migrate from the primary tumor successfully colonize distant sites (7). It is generally recognized that metastatic cells must first detach from the primary tumor mass and be able to survive in an anchorage-independent manner (i.e., survive from anoikis). Subsequently, the surviving cells must navigate the lymphatic and circulatory channels while at the same time evading immune surveillance. Circualting tumor cells must possess the cellular machinery to invade distal organs, implant within local tissues, and initiate de novo tumor growth. While each one of these steps is required for successful metastastic spread of tumor, anchorage-independent survival or resistance to apoptosis or anoikis represents a critical stage in the development of tumor metastasis (6, 7).

The Death Receptor Apoptotic Pathway and Anoikis

Under normal circumstances, epithelial cells undergo anoikis (i.e., detachment-induced apoptosis) on loss of anchorage to the extracellular matrix or when adhesion to the correct substrate is disrupted, primarily by initiating the death receptor-mediated apoptotic pathway. In contrast, malignant epithelial cells with metastatic potential resist anoikis and can survive in an anchorage-independent fashion (6, 8, 9). The death receptor signaling inhibitor, c-FLIP, is highly expressed in several solid and hematologic tumors and, as such, allows tumor cells to escape death receptor-mediated apoptosis (10–13). Inhibition of c-FLIP sufficiently initiates apoptosis, sensitizes cancer cells to death receptor-induced apoptosis or overcomes anoikis-resistance and suppresses cancer metastasis (14–18). Thus, c-FLIP plays a critical role in anoikis resistance and distant tumor formation (14).

The TRAIL/DR5 Death Signaling and Cancer Metastasis

Earlier studies had shown that TRAIL can suppress experimental liver metastasis or contribute to interferon γ-mediated anti-metastatic effects (19, 20). A recent mouse knockout study suggests that TRAIL death receptor (only one in mouse compared with two TRAIL death receptors, DR4 and DR5, in human) plays a suppressive role in cancer metastasis without affecting primary tumor growth (21). In human melanoma tumor samples, a reduced DR5 expression was reported to be associated with metastatic lesions (22). Thus, it appears that the TRAIL/death receptor signaling pathway is associated with suppression of cancer metastasis.

However, other studies from human tissue specimens indicate that DR5 expression is overexpressed in several cancer types and significantly correlated with more aggressive tumor behavior and poor survival of cancer patients (e.g., with breast, lung or renal cell cancer) (23–25). TRAIL was reported to strongly induce the expression of the proinflammatory cytokines interleukin-8 and monocyte chemoattractant protein 1, to enhances the invasion of apoptosis-resistant pancreatic ductal adenocarcinoma cells *in vitro* by upregulation of the urokinase-type plasminogen activator expression and to strongly increase distant metastatic spread of pancreatic tumors *in vivo* (26). Another recent study demonstrated that oncogenic K-Ras and its effector, Raf1, convert death receptors (e.g., Fas and DR5) into invasion-inducing receptors by suppressing the ROCK/LIM kinase pathway, and this is essential for K-Ras/Raf1–driven metastasis formation (27). In this study, Fas ligand and TRAIL were shown to stimulate invasion of colorectal tumor cells and liver metastases in a K-Ras–dependent fashion. Loss of mutant K-Ras switched Fas and TRAIL receptors back into apoptosis mode and abrogated metastatic potential. Raf1 has also been

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shown to be essential for the switch in Fas function, for tumor cell survival in the liver, and for K-Ras–driven formation of liver metastases. K-Ras and Raf1 suppressed Rho kinase (ROCK)/LIM kinase-mediated phosphorylation of the actin-severing protein cofilin. Overexpression of ROCK or LIM kinase allowed Fas ligand to induce apoptosis in K-Ras–proficient cells and prevented metastasis formation, whereas their suppression protected K-Ras–deficient cells against apoptosis (27).

Both FADD and caspase-8 are key mediators of the DR5 death signaling. However, they also exert non-apoptotic functions. For instance, FADD was suggested to promote cell proliferation (28). While caspase-8 loss was shown to result in potentiation of neuroblastoma metastasis (29), increasing number of studies have recently shown that caspase-8 exerts a non-apoptotic function in enhancing cancer cell adhesion, migration, invasion and metastasis, particularly when apoptosis is compromised or inhibited (30–34). The mechanisms by which caspase-8 promotes cell invasion and metastasis involve its interaction with p85 subunit of phosphatidylinositol 3-kinase (31), with Src (32), or with the focal adhesion complex containing focal adhesion kinase (FAK) and calpain 2 (30) and Rab5 activation (34) primarily independent of its catalytic activity.

The DR5/FADD/caspase-8 Signaling in HNSCC

We analyzed the expression of DR5 and caspase-8 by immunohistochemistry (IHC) in primary and metastatic HNSCCs and determined the impact of protein expression on patient survival. IHC analysis revealed a significant loss or downregulation of DR5 expression in matching pairs of primary tumors and lymph node metastasis (LNM) compared to primary tumors without metastasis. A similar trend was observed in caspase-8 expression although this did not reach statistical significance. Univariate analysis indicates that, in HNSCCs with no LNM, higher expression of caspase-8 alone or in combination with higher DR5 expression significantly correlated with better disease-free survival and overall survival (1). These data support an inhibitory role of the DR5/caspase-8 signaling in regulation of cancer development and progression.

Surprisingly, in HNSCCs with LNM, higher caspase-8 expression significantly correlated with poorer disease-free survival and overall survival. In these patients, DR5 levels were not associated with overall survival; however, higher DR5 was significantly associated with a worse disease-free survival. Combined analysis showed that high caspase-8 and DR5 together was significantly associated with poor disease-free and overall survival (1). In agreement, our unpublished data generated from the same cohort of HNSCC tissues show that high FADD expression alone or in combination with high DR5 or caspase-8 expression in HNSCC with LNM was significantly associated with poor disease-free and overall survival. These finding suggest that the DR5/FADD/caspase-8 signaling may have a role in promoting cancer metastasis in the late stage of cancer (e.g., metastasis).

It is possible that in primary tumors the DR5/FADD/caspase-8 signaling predominantly contributes to activation of apoptosis (e.g., anoikis) and therefore can prevent metastasis, but in metastatic tumor cells that have already escaped apoptosis (i.e., are resistant to anoikis), this signaling may be converted to pro-metastatic signaling that promotes invasion and metastasis.

Perspective

In agreement with the foregoing discussion of the potential involvement of the DR5/FADD/caspase-8 signaling in promoting invasion and metastasis of cancer cell, Fas has recently been show to promote tumor growth (35). Moreover, another study has shown that Fas can act as an activator of PI3K by recruiting the Src family member Yes and the

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p85 subunit of PI3K to Fas. This signals for cell invasion via the glycogen synthase kinase 3β pathway and subsequent expression of matrix metalloproteinases, which most importantly, serve as a crucial trigger of basal invasion of glioblastoma *in vivo* (36). Thus, it is plausible that the death receptor signaling pathway (e.g., DR5/FADD/caspase-8) has a dark side in the regulation of cancer development and progression; most likely due to its non-apoptotic function. However, the underlying biology remains to be well elucidated. Uncovering the non-apoptotic function, particularly under apoptosis-compromising conditions (e.g., cancer metastasis), will significantly aid our understanding of the biology of cancer metastasis. Such an understanding may also inform appropriate strategies to exploit this pathway to develop novel therapies against cancer, particularly metastatic cancer. Greater efforts should be dedicated to this line of inquiry.

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