Review Article

INHIBITORS OF APOPTOSIS: STRONG SUPPORTERS FOR ORAL CANCER PROGRESSION

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Abstract:
Apoptosis is a physiological cell suicide program that is critical for the development and maintenance of healthy tissues. Dysregulation of apoptosis is known to occur in cancer and various other diseases. The inhibitors of apoptosis (IAPs) constitute a family of proteins involved in the regulation of various cellular processes, including cell death, immune and inflammatory responses, cell proliferation, cell differentiation, and cell motility. Because of its upregulation in malignancy, it has become of great interest as both a tumor diagnostic and prognostic marker, as well as a new substantial biologic target for future anti-cancer therapies. Abundant literature is available on the structural aspect as well as the possible role of IAPs in various cancers and only few studies have been done in oral cancer. Hence, this review focuses on the role of IAPs in oral cancer.
Keywords: Apoptosis, caspase, cancer progression, anti-cancer therapy

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INTRODUCTION:

Apoptosis, or programmed cell death, is a controlled process of cellular disassembly that occurs in response to internal or external apoptotic signals. It is a greatly synchronized process which is essential for normal development and has numerous functional roles in embryogenesis, tissue homeostasis, and tumorigenesis in multicellular organisms.[1] Apoptosis is regulated by a cascade of cysteine proteases called caspases, which are formed in cells as inactive zymogens and transform to active proteases after proteolysis.[2] The modulation of caspase cascade begins with the activation of an initiator caspase (such as caspases 8 and 9) followed by the activation of an effector caspase (such as caspases 3, 6, and 7).[3] The inhibitors of apoptosis (IAP) are a family of proteins that act as intrinsic negative regulators of the above-mentioned caspase cascade and are the only identified endogenous proteins that interfere with the activity of both initiator and effector caspases.[4] To date 8 human IAP family members have been reported: neuronal apoptosis inhibitory protein (NAIP), X-linked inhibitors of apoptosis protein (XIAP), cellular inhibitors of apoptosis protein 1 (cIAP1), cellular inhibitors of apoptosis protein 2 (cIAP2), survivin, baculoviral IAP repeat-containing ubiquitin-conjugating enzyme, apollon, livin (ML-IAP, KIAP), and IAP-like protein 2.[4] These IAPs are characterized by the presence of one or more 70 to 80 amino acid N-terminal domains, designated as the baculovirus IAP repeat; some bind and suppress activated caspases, including effector caspases 3 and 7 and initiator caspase 9.[5]

NEURONAL APOPTOSIS INHIBITORY PROTEIN (NAIP):

Neuronal apoptosis inhibitory protein, also called Baculoviral IAP repeat-containing protein 1 is a protein that in humans is encoded by the NAIP gene.[6] This gene is part of a 500 kb inverted duplication on chromosome 5q13. This duplicated region contains at least four genes and repetitive elements which make it prone to rearrangements and deletions. The protein encoded by this gene contains regions of homology to two baculovirus inhibitor of apoptosis proteins, and it is able to suppress apoptosis induced by various signals. Alternatively spliced transcript variants encoding distinct isoforms have been found for this gene.[6,7]

CELLULAR INHIBITORS OF APOPTOSIS PROTEIN:

There are two proteins which fall under this category:

1. Cellular inhibitors of apoptosis protein 1 (cIAP1) also known as Baculoviral IAP repeat-containing protein 2 encoded by the BIRC2 gene.
2. Cellular inhibitors of apoptosis protein 2 (cIAP2) also known as Baculoviral IAP repeat-containing protein 3 encoded by the BIRC3 gene.

cIAP1 and cIAP2 inhibit apoptosis by interfering with the activation of caspases. The encoded protein inhibits apoptosis induced by serum deprivation but does not affect apoptosis resulting from exposure to menadione, a potent inducer of free radicals.[8]

X-LINKED INHIBITORS OF APOPTOSIS PROTEIN (XIAP):

X-linked inhibitor of apoptosis protein (XIAP), also known as inhibitor of apoptosis protein 3 (IAP3) and baculoviral IAP repeat-containing protein 4 (BIRC), is a protein that stops apoptosis. In humans, this protein (XIAP) is produced by a gene named XIAP gene located on the X chromosome.[9,10] IAPs were initially identified in baculoviruses, but XIAP is one of the homologous proteins found in mammals.[11] It is so called because it was first discovered by a 273 base pair site on the X chromosome.[9] XIAP is the most potent human IAP protein currently identified.[12,13] XIAP consists of three major types of structural elements. Firstly, there is the baculoviral IAP repeat (BIR) domain consisting of approximately 70 amino acids, which characterizes all IAP.[13] Secondly, there is a UBA domain, which allows XIAP to bind to ubiquitin. Thirdly, there is a zinc-binding domain, or a "carboxy-terminal RING Finger".[12] XIAP has been characterized with three amino-terminal BIR domains followed by one UBA domain and finally one RING domain.[14] Between the BIR-1 and BIR-2 domains, there is a linker-BIR-2 region that is thought to contain the only element that comes into contact with the caspase molecule to form the XIAP/Caspase-7 complex.[15]

SURVIVIN:

Survivin is a protein that inhibits apoptosis and regulates cell division. Survivin is a 15 kb gene and is located on chromosome 17 at band q25.1 It is classified as a member of the inhibitor of apoptosis protein (IAP) family. Survivin inhibits apoptosis, via its BIR domain, by either directly or indirectly interfering with the function of caspases.[16] Survivin is also a chromosomal passenger protein that is required for cell division.[16,17] Survivin is expressed in embryonic tissues as well as in the majority of human cancers, but is not expressed in most normal adult tissues with the exception of the thymus, basal colonic epithelium, endothelial cells, and neural stem cells.[18,19] Survivin contains a single baculovirus IAP repeat and with 142 amino acids, it is the smallest IAP member.[20,21] Survivin has been reported to bind to several caspases but its structure fails to reveal a caspase-binding pocket that is found in other IAP family members. Survivin was also shown to bind to Smac and this binding appears essential for regulating its antiapoptotic activity.[22,23]

APOLLON:

Apollon also known as Baculoviral IAP repeat-containing protein 6 is a protein that in humans is encoded by the BIRC6 gene.[24] This gene encodes a protein with a BIR (baculoviral inhibition of apoptosis protein repeat) domain and a UBCc (ubiquitin-conjugating enzyme E2, catalytic) domain. This protein inhibits apoptosis by facilitating the degradation of apoptotic proteins by ubiquitination.[24]

LIVIN:

Livin also called Baculoviral IAP repeat-containing protein 7 is a protein that in humans is encoded by the BIRC7 gene.[25-27] The protein encoded by this gene is a member of the family of inhibitor of apoptosis proteins (IAP) and contains a single copy of a baculovirus IAP repeat (BIR) as well as a RING-type zinc finger domain. The BIR domain is essential for inhibitory activity and interacts with caspases, while the RING finger domain sometimes enhances antiapoptotic activity but does not inhibit apoptosis alone.[27]

IAP LIKE PROTEIN 2:

IAP like protein 2 (ILP2) is the most recently identified member of the human IAP family.[28] The coding sequence of ILP2 is very similar to the C-terminal half of XIAP, the region containing the BIR3 and RING domains, with 81% identity at the protein level. Over-expression of ILP2 had no protective effect on death mediated by Fas or tumour necrosis factor, but prevented death induced by Bax or caspase 9 in vitro leading to the conclusion that ILP2 blocks the intrinsic apoptotic pathway by directly inhibiting caspase 9.[29]ILP2 was identified during genome analysis of XIAP. The most significant difference between ILP2 and XIAP is that ILP2 lacks the first two N-terminal BIR domains present in XIAP.[28,29]

INHIBITORS OF APOPTOSIS AND ORAL CANCER:

Carcinogenesis is a multistage process involving the activation of oncogenes and the inactivation of tumour suppressor genes. Most human tumours are characterised by an imbalance of regulatory mechanisms controlling cell cycle progression, cell death/viability balance, and apoptosis.[30] Apoptosis has become a basic tool in developing cancer research and establishing new cancer strategies. Aberrations of this process leading to aberrantly reduced cell death are thought to participate in cancer by promoting increased resistance to therapy and favouring the insurgence of transforming mutations.[31] Considerable interest has recently focused on the identification of regulators of apoptosis, which may potentially influence the cell death/cell viability balance in cancer. In addition to pro- and antiapoptotic bcl-2 molecules, a second gene family of inhibitor of apoptosis (IAP) has been recently identified. However, there are very few studies which have focussed on the role of apoptotic inhibitors in oral squamous cell carcinoma.

X-LINKED INHIBITORS OF APOPTOSIS PROTEIN (XIAP) IN ORAL CANCER:

X-linked inhibitor of apoptosis (XIAP) is a member of the inhibitor of apoptosis protein family, which is associated with cell survival by blocking caspase-mediated apoptosis. XIAP is expressed in various malignant tumors. The overexpression of XIAP has been reported to be a poorer prognostic factor in various malignancies. However, the prognostic value of XIAP expression in patients with oral cancer is not still clear.[32] Tamatani T et al evaluated the expression of XIAP protein in oral squamous cell carcinoma (OSCC) to elucidate the relationships among the XIAP expression, clinical stages, histological differentiation and classification of invasion mode. The expression of XIAP was detected in all cancer cells, but not in normal cells. Immunohistochemical analysis of 85 cases of OSCC showed that 73 (86%) cases expressed XIAP. There was no relationship between XIAP expression and clinical stages, or classification of invasion

mode. They found significant differences between XIAP expression and histological differentiation. Most of non-staining and weakly staining of cancer was well differentiated. In contrast, intense and extensive staining was frequently found in poorly differentiated cancer. The results of this study suggested that the expression of XIAP in OSCC could be related to histological differentiation.[33] In a study by J.F Wang, XIAP expression was detected by immunohistochemistry in 28 cases OSCC tissues and 10 cases of normal oral mucosa tissues: XIAP expression in 23 of 28 (82.14%) of OSCC, and 3 of 10 (30.0%) of the normal oral mucosa tissues. The positive rate and expression level of XIAP protein in OSCC were higher than the normal oral mucosa tissues and XIAP expression was significant difference between pathological grades.[34] In another study by Yang XH et al, expression of XIAP was examined both before and after chemotherapy and was correlated with chemotherapy response, clinicopathology parameters and clinical outcomes of the patients. They found that XIAP was expressed in 17 (20.83%) of the 60 advanced HNSCC samples and the expression was significantly associated with cisplatin resistance and poor clinical outcome. Cisplatin-based chemotherapy induced XIAP expression in those post-chemotherapy samples was further associated with poorer clinical outcome. Multivariate analysis demonstrated that only alcohol consumption, lymph node metastasis and XIAP level were independently associated with the prognosis of advanced HNSCC patients. Inhibiting XIAP expression with siRNA in XIAP overexpressed HNSCC cells remarkably increased their sensitivity to cisplatin treatment to nearly a 3 fold difference. These results of this study demonstrate that XIAP overexpression plays an important role in the disease course and cisplatin-resistance of advanced HNSCC. XIAP is a valuable predictor of cisplatin-response and prognosis for patients with advanced head and neck cancer. Down-regulation of XIAP might be a promising adjuvant therapy for those patients of advanced HNSCC.[35]

CELLULAR INHIBITORS OF APOPTOSIS (CIAP) IN ORAL CANCER:

cIAP-1, an apoptosis inhibiting protein, has been suggested to play important roles in the development of cervical and esophageal squamous cell carcinomas (SCCs). In order to clarify the subcellular localization of cIAP-1 and to investigate its clinicopathological significance in head and neck SCCs (HNSCCs), Tanimoto T et al examined cIAP-1 expression in four oral SCC cell lines by immunocytochemistry and Western blot. Expressions of nuclear and cytoplasmic cIAP-1, caspase-3, and Smac/DIABLO were also examined immunohistochemically in 57 cases of the HNSCCs. cIAP-1 expression was detected in HSC-2, HSC-3, and HSC-4 cells by immunohistochemistry and Western blot. In HSC-2 and HSC-4 cells, cIAP-1 was detected in both the nuclear and cytoplasmic fractions. Nuclear cIAP-1 expression was positive in 17 (30%) of HNSCCs, was correlated with lymph node metastasis and advanced disease stage, and tended to be correlated with poor patient prognosis. Cytoplasmic cIAP-1 expression showed similar but weaker clinicopathological correlations. Nuclear cIAP-1 expression was inversely correlated with caspase-3 expression, but was correlated with Smac/DIABLO expression. Nuclear cIAP-1 expression appears to be a useful marker for predicting poor patient prognosis in HNSCCs, and may play roles in HNSCCs through the signaling pathway mediated by Smac/DIABLO and caspase-3.[36]

The possible significance of cIAP-1 expression in cervical lymph node metastasis of tongue squamous cell carcinoma (SCC) was investigated by Qi S et al. Seventy-five tongue SCCs were analyzed by immunohistochemistry. cIAP-1 immunoreactivity patterns were nuclear in 38 (51%), cytoplasmic in 47 (63%), and concurrent in 37 (49%) cases. Nuclear,

cytoplasmic and concurrent cIAP-1 immunoreactions were significantly correlated with lymph node metastasis in tongue SCCs. The cleaved caspase-3, which is a marker of tumor apoptosis, and Ki-67 index, which is a marker of tumor proliferation, were immunohistochemically examined in 21 tongue SCCs with concurrent nuclear and cytoplasmic cIAP-1 expression and with metastasis, and in 23 tongue SCCs without concurrent nuclear and cytoplasmic cIAP-1 expression and without metastasis. Concurrent cIAP-1 expression was inversely correlated with caspase-3, but was positively correlated with Ki-67 expression. The mode of invasion was associated with lymph node metastasis and differentiation, but was not correlated with cIAP-1 expression. There was no statistically significant correlation between nuclear or cytoplasmic cIAP-1 expression and the clinicopathological factors of gender, age, clinical stage or differentiation. These results suggest that both patterns of cIAP-1 are useful markers for predicting cervical lymph node metastasis in tongue SCC.[37]

The effects of cIAP2 downregulation on 5-FU sensitivity and apoptosis were evaluated by Nagata M et al. An immunohistochemical analysis of cIAP2 and related proteins, cIAP1 and X-linked IAP, was performed in 54 OSCC patients who were treated with 5-FU-based chemoradiotherapy and surgery. The downregulation of cIAP2 significantly enhanced the sensitivity of the 5-FU-resistant cells to 5-FU, with a significant increase in apoptosis. The immunohistochemical analysis demonstrated a high cIAP2 tumour expression to significantly correlate with the pathological response to chemoradiotherapy. Furthermore, a Cox regression analysis revealed the cIAP2 expression status and the pathological response to chemoradiotherapy to be significant prognostic factors for OSCC patients. These novel findings demonstrate that cIAP2 may represent a potentially useful therapeutic target for improving the treatment and survival of OSCC patients, particularly in the setting of 5-FU resistance.[38]

SURVIVIN IN ORAL CANCER:

Survivin is a new and structurally unique member of the inhibitor of apoptosis (IAP) family. Unlike other IAP proteins, survivin is found during embryonic and fetal development. However, survivin is completely down-regulated and undetectable in normal adult tissues and becomes prominently re-expressed in all of the most common human cancers.[39] It's overexpression has been correlated with poor prognosis, cancer progression and drug resistance.[40] O'Connor DS et al showed in their in vitro and in vivo studies that surviving is over-expressed in cancer which is physically associated with the cyclin dependent kinase p34cdc2 on the mitotic apparatus, and is phosphorylated on Thr34 by p34cdc2-cyclin B1.[41] A series of 135 cases of squamous cell carcinoma including 46 oral squamous cell carcinomas and 89 cutaneous squamous cell carcinomas were studied by Lo Muzio et al for survivin expression by immunohistochemistry. Survivin was found in 57 cases (64%) of skin squamous cell carcinoma and 26 cases (56%) of oral squamous cell carcinomas. In contrast, normal oral epithelium, normal skin epithelium, and skin adnexa did not express survivin. Survivin expression significantly segregated with high-grade and undifferentiated tumours with size >1.5 cm and invariably associated with lymph node metastasis.[42]

In another study conducted by Lo Muzio L et al, 110 cases of oral squamous cell carcinoma (SCC) together with six lymph nodes and one distant metastatic lesion were evaluated for expression of surviving by immunohistochemistry. In total, 91 cases (82.7%) of carcinoma and all metastasis (seven cases, 100%) were positive for survivin expression. In contrast, normal oral epithelium did not express survivin. There was no significant correlation between

survivin expression and age, sex, tumour size, the presence of lymph node and distant metastases. Survivin expression was increased in poorly differentiated tumours, even if differences were not statistically significant.[31] Lin CY et al studied the expression of surviving in 62 cases of oral epithelial dysplasia and 96 cases of oral squamous cell carcinoma immunohistochemically. Cytoplasmic survivin staining was detected in 60 of the 62 (97%) oral epithelial dysplasia specimens and 94 of the 96 (98%) oral squamous cell carcinoma specimens but not in adjacent normal oral mucosal tissues.[43] Jane C et al evaluated the expression of survivin in 38 patients with primary oral squamous cell carcinoma and 17 patients with leukoplakia by using immunohistochemical staining method. In oral leukoplakia, survivin expression was found to be localized mainly in the parakeratin/keratin layer and the prickle cell layer. Survivin expression was found to increase with increased grade of malignancy. Increase in survivin expression was statistically most significant.[30] A series of oral biopsy specimens of 19 cases (12 men and 7 women) of oral cancer was studied by Jinbu Y et al for survivin expression and its relation with the clinicopathologic characteristics. The overall survivin positivity was 58%. The percentage of survivin-positive specimens in the T1+T2 group was significantly higher than that in the T3+T4 group and the percentage of survivin-positive specimens in the N0 group was also significantly higher than that in the N+ group. A slightly higher percentage of survivin-positive specimens were observed in the gingival cancer group compared with the tongue cancer group.[39] In another study, Kim YH et al did the assessment of the diagnostic and prognostic significance of survivin in a series of 38 primary oral squamous cell carcinomas through immunohistochemistry. Survivin expression was detected in all oral squamous cell carcinomas at a varying level but not observed in normal gingival keratinocyte cells. Clinicopathological analysis revealed a significant correlation between survivin expression and lymph node metastasis and proliferation.[44] Preuss SF et al conducted a multicentre retrospective study on 106 consecutive oropharyngeal cancer patients. Human papillomavirus sequences were detected by nested PCR protocols. Survivin expression as a surrogate marker for HPV status were analysed by immunohistochemistry. Sequences of high-risk HPV were detected in 29% of cases. Prominent cytoplasmatic expression of survivin was found in 58% of cases and nuclear expression of survivin was found in 19% of the survivin-positive tumours. Nuclear expression of survivin was significantly correlated with HPV-negative tumours and with a poor disease free survival rate.[40]

LIVIN IN ORAL CANCER:

Zong ZH et al investigated the expression of the newly found inhibitor of apoptosis protein Livinalpha and Livinbeta and their gene expression in human oral squamous cell carcinoma. Twenty specimens of human squamous cell carcinoma(SCC), 15 cases of benign cysts, 10 cases of normal oral mucosal tissues adjacent to the cancerous lesions were examined. Polymerase chain reaction with reverse transcription (RT-PCR) and Western blot analysed were used to detect mRNA and protein expression of Livin respectively. Livin protein and mRNA expression was detected in 19 SCC tissues,14 benign cysts and 10 normal oral mucosal tissues adjacent to the cancerous lesions.But the expressions were significantly higher in oral SCC than in benign cysts and normal oral mucosal tissues. These results suggested that Livin may play an important role in the tumorigenesis and development of human oral squamous cell carcinoma.[4] Jiang L et al studied the expression of livin at the invasive tumor front (ITF) of oral squamous cell carcinoma. Forty-eight samples of oral squamous cell carcinoma were graded according to invasive front grading (IFG).

The expression of livin was evaluated at the ITF and other parts of the same tumor using immunohistochemistry. Significant difference in the pathological grades was found between the ITF and the other parts of oral squamous cell carcinoma. The expression of livin at the ITF was significantly stronger than that in the other regions. A significant positive correlation was noted between livin expression and the IFG score.[46]

CONCLUSION:

IAPs are much more than just “inhibitors of apoptosis”. An involvement with signal transduction cascades regulating apoptosis, proliferation, cell survival and migration suggests that IAPs are strong supporters of cancer progression.

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