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Anti-Apoptotic Gene: Survivin

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Abstract

In developing countries where most people live in rural areas, oral cancer tends to be a challenge in diagnosis and management, as most of the cases present at a later stage. Carcinogenesis is a multifactorial process which involves the activation of oncogenes and the inactivation of tumour suppressor genes. Biomarkers are important in establishing an accurate diagnosis and also can provide prognostic data. Survivin is a member of the inhibitor of apoptosis (IAP) protein family that inhibits caspases and blocks cell death, is highly expressed in most cancers and is associated with a poor clinical outcome. It orchestrates several important mechanisms to support cancer cell survival including inhibition of apoptosis and regulation of cell division. These feature makes survivin an ideal target for cancer therapy. The present review focuses on role of survivin cancerous and pre-cancerous lesions of oral cavity.

Keywords: Survivin, Apoptosis, Oral Squamous Cell Carcinoma

Introduction

Oral squamous cell carcinomas (OSCCs) account for approximately 5,00,000 new cases worldwide, making them the 6th most common cancer type in world and they are the third most common cancer in developing countries with high incidence in South East Asia and India.[1-4] OSCC is associated with greater mortality and morbidity due to its highly invasive nature that often invades neighboring tissues, and can metastasize distant organs.[5-6] Despite advances in treatment, the overall 5 year survival rate for OSCCs is merely 50% with most patients at high risk for loco-regional recurrence and distant metastasis.

Apoptosis has become a basic tool in developing cancer research and establishing new cancer strategies. Apoptosis or programmed cell death is a genetically controlled process, which maintains developmental morphogenesis and homeostasis of differentiated organisms by removing senescent, unneeded, or dangerous cells. Apoptosis is regulated by a cascade of cysteine proteases called caspases, which are formed in the cells as inactive zymogens and transform to active proteases after proteolysis. Organisms have to firmly modulate and tightly control the caspase cascade, which 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).[7]

IAPs (Inhibitor of apoptosis protein) are a family of highly conserved cell death inhibitors that have been found in yeast, invertebrates, and vertebrates. IAPs were first discovered in baculoviruses, where they were shown to be involved in suppressing host cell death response to viral infection.[8] Presently, 8 human IAP family members have been reported. These IAPs are characterized by the presence of 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 an initiator caspase 9.

Survivin is a recently characterized smallest member of the IAP family of proteins, a cluster of genes playing an important role in apoptosis regulation, involving both in the cell death regulation and in different aspects of cell division.[9]

Survivin

Survivin is the smallest member of the mammalian IAP family containing only a single N-terminal baculovirus IAP repeat (BIR) domain combined with long C-terminal α-helix coiled region. The gene encoding Survivin is located on chromosome 17q25 in humans.[9]

Survivin Functions

1. Regulation of mitosis

Survivin localizes to the apparatus of mitotic bundle. There was catastrophic defect of mitosis in survivin negative embryos. Antisense or dominant-negative mutants showed failure in cytokines and polyploidy. Defects in spindle assembly, chromatid separation and spindle-checkpoint activation after antibody microinjection.

2. Inhibitor of cell death

Survivin inhibits the intrinsic and extrinsic pathways of apoptosis. In transgenic mice it has shown resistance to apoptosis. There was increased sensitivity to apoptosis in mice showing survivin negativity. Spontaneous apoptosis induced by antisense, dominant-negative mutants or ribozyme. Survivin has shown to be associated with caspases and SMAC/DIABLO thereby inhibiting the cell death signaling.[10]

3. Role of survivin in cell division

Survivin plays an important role in cell division by the regulation of mitosis. It is expressed mostly in G2-M phase in a cell cycle dependent manner. Survivin interacts with tubulin and localizes to the mitotic spindle indicating its involvement in the regulation of mitosis. It plays an important role in centrosome functions, microtubule assembly during metaphase and anaphase and spindle checkpoints. Depletion of survivin causes defective cell division. Survivin deficient cells frequently fail to complete both chromosome segregation and cytokinesis during mitosis.[11]

4. Role of Survivin in apoptosis

Apoptosis can be triggered with the two major types of stimuli, external and internal. The extrinsic apoptotic pathway initiates by the activation of death receptors (CD-95/ Fas and TNFα receptors) through external signals following activation of initiator caspase-8. The intrinsic

apoptotic pathway initiates due to intracellular signals that act through mitochondria. Survivin can be co-immuno-precipitated with caspases-3, -7, and -9 and it suppresses apoptosis induced by over expression of these caspases, implying that survivin also is a caspase inhibitor. It also inhibits cell death by interfering with caspase-9 processing, the main inhibitor in intrinsic pathway of apoptosis.[11]

Survivin expression has been shown in various preneoplastic and benign lesions including polyps of the colon, breast adenomas, and nearly all cases of Bowen's disease, cervical dysplasia and hypertrophic actinic keratosis suggesting that expression of survivin may occur early during malignant transformation.[12]

The finding of survivin expression in normal tissue is not completely surprising. Although most studies employing immunochemistry techniques reported no survivin expression in clinically normal mucosa, several studies employing this technique demonstrated survivin expression in basal and parabasal cells of oral mucosa. Survivin has also been demonstrated in a number of normal tissues, particularly in those with high proliferation rate, as it is critical for mitotic cell division and is unregulated in mitosis.[13]

It was found that with the transition from normal mucosa to dysplasia to carcinoma, both the number of cells expressing survivin and the intensity of staining are increasing. This suggests that with increase in the grades of dysplasia and the degree of differentiation, the cells retain the self sufficiency potential and resist the apoptotic signals. Survivin protects against apoptosis and regulates the progression of cell cycle; therefore, it is conceivable that, survivin plays an important role in the pathogenesis of OSCC. All these findings indicate that the increase in survivin expression is the early event of oral mucosa oncogenesis and the intensity of survivin expression is continuously increasing with the development of the disease. Therefore survivin can be regarded as a biomarker for monitoring oral potentially malignant lesions.

Conclusion

Survivin expression in OSCCs may be helpful in identifying patients at risk of more aggressive and disseminated disease. This may be relevant for the institution to conduct closer follow-up protocols and/or use alternative combined therapeutic regimens. These findings reiterate the importance of deregulation of apoptosis as a critical pathogenetic component of tumour progression, and identify survivin as a potential novel molecular marker of aggressive neoplasia.

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