EDITORIAL

Use of Tilapia Hepcidin in Oral Cancer Therapeutics: A Proposal

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Tilapia hepcidin (TH), an antimicrobial peptide (AMP) derived from tilapia (*Oreochromis mossambicus*) forms an important component of the fish innate immune defense.[1] However, the functionality of TH is not just limited to its antimicrobial actions, significant applications in cancer research remain an area to be explored. Antimicrobial peptides derived from fish and shrimp demonstrated anticancer activities in addition to their previously discovered antimicrobial action. Three hepcidin-like AMPs can be isolated from tilapia, namely TH1-5, TH2-2, and TH2-3. Of these, TH1-5 and TH2-3 have shown potent antitumor activity.[2]

The AMPs from fish exhibit numerous activities that make them promising candidates in cancer therapeutics. The antineoplastic effects of TH are summarized in Flowchart 1. Tilapia hepcidin causes inhibition of tumor cell proliferation.[3] The growth-inhibiting the potential of TH2-3 and TH1-5 is documented in the *in vitro* studies by Chen et al.[3] and Chang et al.[2] The antineoplastic effect was first shown on human hepatic fibrosarcoma cells.[3] They are also known to prevent tumor invasion and metastasis by affecting cancer cell motility.[4] This characteristic is supposedly due to electrostatic interactions among TH-treated cancer cells, which are not favored due to the neutral charge conferred on healthy cells by zwitterionic nature of their major membrane components such as phosphatidylethanolamine (PE), phosphatidylcholine (PC), and sphingomyelin (SM), and are therefore less attractive to TH2-3 and other antimicrobial peptides![5,6] TH induces tumor cell necrosis when treated at high concentration, but apoptosis when treated at low concentration.[2] The lytic action of TH2-3 can be accounted to the significant disruption of the cancer cell membrane and formation of holes leading to an outflow of cellular contents, eventually leading to targeted cell death.[3] Certain subgroups of AMPs, in

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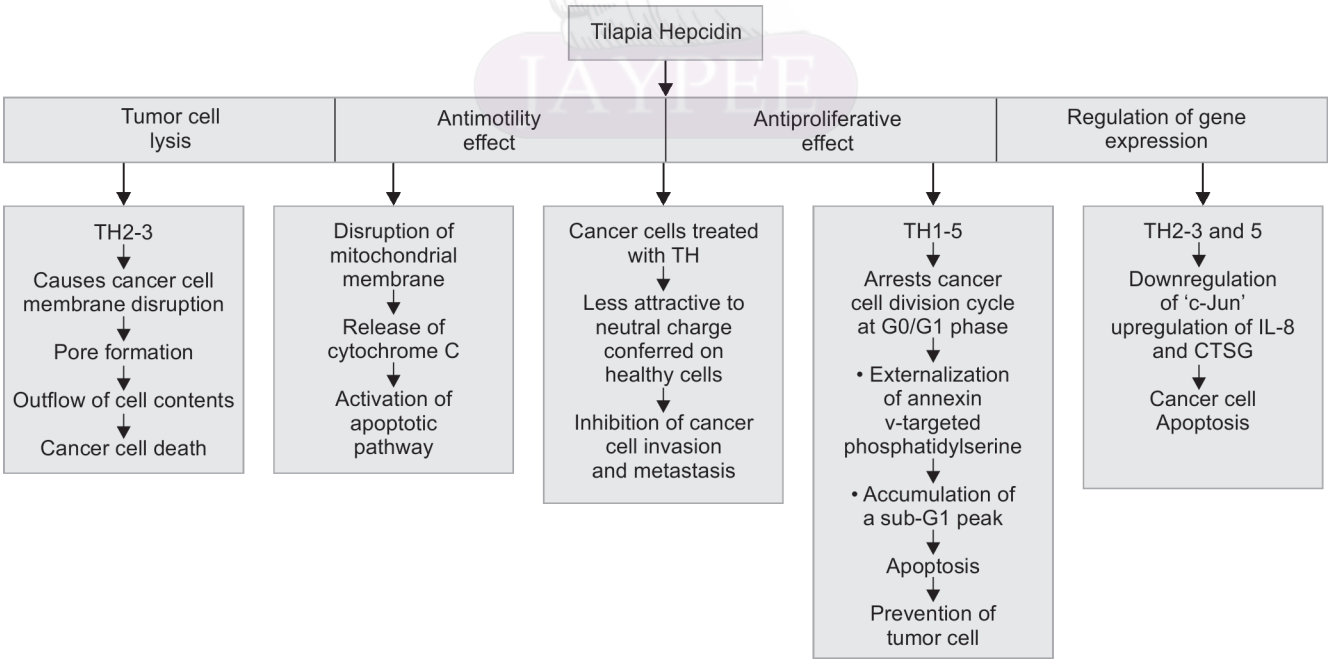
Flowchart 1: Antineoplastic effects of tilapia hepcidin



addition to membrane disrupting action also induce disruption of mitochondrial membrane and release of cytochrome C which then activates apoptotic pathways.[7] TH1-5 selectively induces impediment of cell cycle progression in cancer cells by arresting the cycle at G0/G1 phase and triggers apoptosis as displayed by the externalization of annexin v-targeted phosphatidylserine and accumulation of a sub-G1 peak.[2] In addition to this, TH also exhibits regulatory effects on certain genes. TH2-3 downregulates one of the apoptosis genes "c-Jun", whereas TH1-5 cause upregulation of IL-8 and CTSG in human fibroblast sarcoma cells and IL-2 and CAPN5 in Hela cells.[2,3] TH2-3 in lipopolysaccharides stimulated cells reduces the release of "tumor necrosis factor (TNF)-α" and other cytokines through a cyclooxygenase-2 and phosphodiesterase 4D mechanisms.[8] In summary, TH work on the popular and well-known mediators of oral cancer progression!

Despite the tremendous advances in cancer treatment, oral squamous cell carcinoma continues to be among the most common malignancies of head and neck region, associated with poor prognosis and high mortality. Although past several decades have witnessed great strides in anticancer therapy, these strategies are still compromised due to the emergence of resistance to conventional chemotherapeutic agents and paucity of specificity against the relatively slow dividing "oral cancer stem cells" which are the hidden culprits! These voids in the treatment strategies demand additional alternative therapies and adjuvant chemo-therapeutic agents with novel antitumor mechanisms like selective affinity to cancerous cells.[9] TH derived from fish appears to be a candidate for oral cancer therapeutics. TH is bestowed with cytotoxic mechanisms that involved isolation of cancer cells, affect the motility of cancer cells preventing invasion and metastasis, and regulate gene expression that promotes "selective apoptosis" of cancer cells. Unlike other chemotherapeutic agents that typically fail to distinguish cancer cells and normal cells, TH1-5 shows accentuated lytic action toward cancer cells![2,10]

These results are sufficient to propose TH as a possible anti-cancer agent for primary treatment or adjuvant treatment in oral cancer. More recently, nanotechnologists have incorporated TH into liposomal formulations and enhanced the therapeutic effect of "epirubicin" on human tongue squamous cell carcinoma (SCC-15), human embryonal carcinoma cells, and Hela cells.[11,12] It led to a rise in cell death through reduced epirubicin efflux via reactive oxygen species (ROS)-mediated suppression and concomitant initiation of the mitochondrial apoptosis pathway. Thus, TH affects these cells by suppressing the multidrug resistance transporters, apoptosis, autophagy, and/or necroptosis.[12] TH may have a scope as an adjuvant or primary chemotherapeutic agent in oral cancer therapeutics.

However, to date, the antineoplastic activity of TH has been demonstrated on other cancer models, and its effect has just been tested on SSC-15 using only epirubicin. Moreover, owing to the anatomical differences, prognosis, genetics, and molecular pathways, tongue cancer has been categorized as a separate entity from cancers of other intraoral sites.[13] Thus, future research work should be focused on various other oral cancer models. Thorough exploration should be carried out using TH alone and/or in combination with other ROS-inducing anticancer agents like cisplatin and carboplatin, which might exceed the threshold for ROS resulting in activation of multiple cell death pathways. Thus, TH is needed to be scrupulously studied and clinically validated in combination with routinely used chemotherapeutic agents to treat oral cancer to establish it as either adjuvant or as a primary line of treatment in oral cancer therapeutics. This may also direct toward a novel strategy for effective reversing of multidrug resistance, which is a major obstacle in oral cancer treatment.

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