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Mini Review

Antimicrobial Peptides in Bladder Cancer

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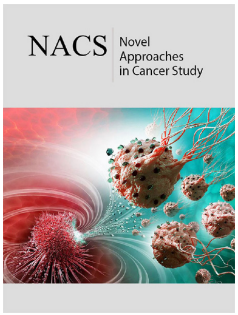

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Introduction

Antimicrobial peptides are important components of the innate (non-specific) immune defense against microbial pathogens in a wide range of organisms including humans [1,2]. Mammalian cells secrete different kinds of AMPs, such as Human Beta-Defensins (HBD-1 or HBD-4) in the epithelium and leukocytes, histatins in saliva, and cathelicidins (CAP18 or CAMP) in neutrophils and the epithelium [3,4]. Mycobacteria trigger epithelial cells to express AMPs. AMPs have nonspecific cytotoxicity against a wide range of normal and malignant targets, and direct lyse mycobacteria by permeabilizing the cellular membranes [5,6]. Some bacteria protect themselves against AMPs by secreting special proteins that inhibit their function, such as Streptococcal İnhibitor of Complement (SIC) and D-Alanine: D-Alanyl carrier protein ligase (DltA) [7-10]. Bacillus Calmette-Guérin (BCG) is commonly used as the most effective immunotherapeutics for high-risk non-muscle-invasive bladder cancer patients. Although BCG is more effective than the other chemotherapies, innate immune responses involving Antimicrobial Peptides (AMPs) cause BCG failure and unwanted side effects. After intravesical application in the bladder, BCG first directly contacts with the bladder urothelium, and the second step is BCG uptake by bladder cancer cells (internalization), probably by endocytosis. The innate immune response acts against BCG to sterilize the urinary tract, and some of the effectors involved in this innate response to BCG are Antimicrobial Peptides (AMPs). It was shown that rBCG treatment induced higher secretion of AMPs by the bladder cancer cells compared to BCG treatment and rBCG exerts a direct anti-proliferative effect on human bladder cancer cells. Therefore, it is believed that the therapeutic efficacy of BCG could be maintained or improved with lower doses of rBCG without the severe side effects or infection associated with the administration of high-dose BCG.

During initial recognition of pathogens like BCG mycobacteria, Toll-like receptors 2 and 4 (TLR2 and TLR4, respectively) are activated to elicit immune responses [10,11]. Activation of TLRs releases Antimicrobial Peptides (AMPs) and pro-inflammatory cytokines via nuclear factor-.B (NF-.B) pathways [12,13] and Mitogen Activated Protein Kinases (MAPK) pathways, leading to modulation of transcription of inflammatory genes [14,15]. MAPK pathways are crucial to mycobacteria induced macrophage signaling via TLRs [14,15]. Similar to the molecular mechanisms by which mycobacteria upregulates AMPs in epithelial cells, MAPK pathway activation contributes to the regulation of inflammatory processes in BCG-infected epithelial cells. HBD-2 participates in anti-bactericidal activities directed against BCG, which is mediated by MAPK signaling pathways regulating HBD-2 expression in human epithelial cells during BCG infection [16]. The recent study demonstrated that MEK inhibitors enhance BCG treatment-induced tumor cell death via the blockage of AMPs release. The enhanced antitumor effects of BCG in bladder cancer cells are associated with the inhibition of TLR2-mediated MEK pathway. It seems that the activation of intracellular signaling pathways in response to BCG infection as a novel strategy to boost BCG treatment efficacy in urothelial

carcinomas. It was reported that MEK inhibitors enhance sensitivity to BCG treatment in bladder cancer cells, furthering that the understanding of the underlying mechanisms blocking TLR2-derived AMPs release. Although MAPK signaling is implicated in the promotion of cell survival and proliferation, BCG-induced AMPs rely more heavily on TLR2-ERK signaling for the innate and adaptive immune responses. The combination of BCG plus MEK inhibitors may be useful as a salvage regimen in BCG failures. Low dose BCG treatment may be valuable for BCG refractory bladder cancer patients. Magainin II belongs to a family of antimicrobial peptides and was originally isolated from the skin of the African clawed frog, Xenopus laevis [17]. Magainin II provides promising antineoplastic activity, which renders it potentially useful as an agent for intravesical bladder tumor therapy. Besides their well-known antimicrobial activity, recent studies have also reported a significant cytotoxic effect of magainin II against a wide range of cancer cell lines including melanoma, breast and lung cancers as well as lymphomas and leukemias [18-21]. It was reported that significant antitumor activity of the structurally and functionally related antimicrobial peptide Magainin II against bladder cancer cell lines *in vitro*. Thus, Magainin II as an AMP may play a potential role as an intravesical drug in superficial bladder cancer and represents a novel therapeutic strategy.

Cecropin A and B exert strong antibiotic activity against both Gram-positive and -negative bacteria in micromolar concentrations [22,23]. Cecropins have the ability to form specific amphipathic alpha-helices which allow them to target nonpolar lipid cell membranes. Upon membrane targeting, they form ion-permeable channels subsequently resulting in cell depolarization, irreversible cytolysis and finally death [22,24]. Besides their well-known antimicrobial properties, recent studies have demonstrated specific tumoricidal activity of both Cecropin A and B against mammalian leukemia, lymphoma and colon carcinoma cell lines [25,26] as well as small cell lung cancer [27] and gastric cancer cells [28]. *In vivo*, Cecropin B improves survival of mice bearing ascitic colon adenocarcinomas [26]. Transfection of human bladder cancer cells with Cecropin genes reduces their tumorigenicity in nude mouse models [29]. It was reported that Cecropin A and B exert significant selective cytotoxic and antiproliferative efficacy in bladder cancer cells while sparing targets of benign murine or human fibroblast origin. Their unique mechanism of action appears to depend at least partially on the disruption of target cell membranes resulting in irreversible cytolysis and cell destruction. Both, Cecropin A and B are promising candidates for further preclinical evaluation as intravesical treatment options in non-muscle invasive bladder cancer [30,31].

Conclusion

In summary, antimicrobial peptides are especially promising candidates for anticancer therapy in humans because they demonstrate several unique features; their selectivity for malignant cells and their potentially pronounced lytic activity against high-grade tumor cells allow for an optimal therapy *in vivo* with low therapeutic concentrations and limited side effects. Although the molecular basis for this selective antitumor activity of antimicrobial peptides has not yet been completely understood, AMPs may play a potential role in non-muscle invasive bladder cancer and represents a novel therapeutic strategy.

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