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Editorial Open Access

Restoration of Tight-Junction Function: A New Therapeutic Approach for the Treatment of Cancer

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Cancer affects a significant proportion of the population of the United States and the rest of the world. In the U.S. approximately 12 million people were directly affected by cancer in 2010 [1]. In a significant percentage of these patients, the disease will become invasive and may eventually be the primary cause of death. Classical treatment of cancer involves surgery, radiation and chemotherapy. However, chemo and radiation therapies cause more harm rather than help in the long run as it is becoming evident that radiation/chemo therapies induce mutations that could transform the tumor into a drug-resistant and metastatic cancer [2-4]. Recent advances in cancer biology provide a hope for the development of novel, personalized and targeted therapy for cancer patients. Among many new directions of research in cancer, the understanding of the mechanisms that transform a localized tumor into an invasive one is the most exciting.

Although cancer is frequently considered as a disease of abnormal proliferation and accelerated abnormal growth, cancer progression is not determined solely by proliferative advantage of malignant cells within a tumor [5]. Other factors such as resistance to apoptosis and ability to bypass senescence pathways also contribute significantly to the process [6]. Correct adhesion between adjacent epithelial cells is important in determining the normal structure and function of epithelial tissues [7]. Accumulating evidence suggests that dysregulated cell-cell adhesion is associated with development and progression of most epithelial cancers [8].

Cell-cell adhesion is a critical component for the assembly of coherent sheets of barrier-forming epithelial cells that eventually line most organs, ducts and lobules. However, it is now understood that cell-cell contacts are not static structures that maintain barriers by just holding cells together. These contacts undergo constant remodeling to allow extrusion of apoptotic cells and to replace them with newly formed epithelial cells without the loss of barrier function. Cell-cell contacts are also remodeled to meet special physiological and developmental needs such as puberty, pregnancy, lactation, or involution. During wound healing, epithelial cells undergo coordinated movement and proliferation to bridge the wound, and establish new cell-cell contacts with epithelial cells from the opposing side of the wound [9-11].

Epithelial cell-cell contacts consist of three main adhesive structures: tight junctions (TJs), adherens junctions and desmosomes, as well as gap junctions. In polarized epithelial cells the TJs and adherens junctions are asymmetrically distributed at the apical region of the lateral membrane. This asymmetry forms the apical junctional complex, which encircles the apex of the cells and marks the border between apical and basolateral membrane domains [9,12]. These adhesive structures are composed of integral transmembrane proteins such as claudins or occludin that link the neighboring cells through homophilic and heterophilic interactions. These transmembrane proteins are anchored to cytoskeleton by zonula occludens proteins, which also organize signaling complexes and anchor cell-cell contacts to the actin cytoskeleton [13,14]. Especially, zonula occludens-1 (ZO-1) plays a key role in organizing TJs by serving as a scaffold and providing multiple interaction domains where several transmembrane and signaling proteins can bind to form the TJ structure [13,15,16]. As the most apical structure between epithelial and endothelial cells, TJs control paracellular diffusion of ions and certain molecules [17]. In addition, TJs play a vital role in maintaining cell to cell integrity and cohesion of the organ lining [18]. The loss of cohesion between tight junctions could lead to dysplastic changes, which may eventually transform into cancer [19].

It must be noted that a relationship between TJ proteins and epithelial cancers is complex. An intact and functional TJ complex acts as a barrier to the initiation and progression of epithelial cancers by regulating important processes such as cell polarity, cell fate and cell movement. However, any imbalance in the protein components of this complex (whether increased or decreased) might disrupt the homeostatic control required to maintain the tissue in its differentiated state. The imbalance can also alter cell-cell and cell-extracellular matrix interactions, and cause disordered organ lining that makes cells chronically leaky to mitogens and growth factors. Together, these events can promote cancer formation in premalignant epithelial tissues [7]. Disruptive changes in TJ complex can also alter cell adhesion, free tumor cells from both neighboring cells and the underlying matrix; and confer onto them a migratory or invasive characteristics [20]. The role of individual TJ proteins in this process is suggested by the following few examples from a large body of evidence. The role of claudin-1 in the control of cell fate is indicated by increased expression in senescent epithelial cells and reduced expression in invasive cancers [21]. Decreased ZO-1 expression correlates with decreased glandular differentiation of breast tumor specimens [22]. ZO-1 and ZO-2 also regulate cell cycle progression and proliferation in a cell density-dependent manner through transcription factors such as ZONAB [23].

A large majority of cancers affecting elderly population are epithelial, and display dysregulated cell-cell adhesion. With better understanding of the factors and mechanisms involved in dysregulated cell-cell adhesion, it is becoming apparent that therapies specifically directed at restoring normal TJ function might be beneficial in halting the progression of epithelial tumors and in restoring normal cell-cell adhesion patterns. Unfortunately, the delivery of the TJ-targeting therapeutic agents to the site of action can pose a major problem. The agent must traverse epithelial and/or endothelial barriers to reach the site of action. Since the TJ is the primary regulator of paracellular transport across such cells, successful drug delivery may require modulation of TJ proteins to allow drug molecules to pass

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[24]. However, as noted before, disruption of TJ proteins purely for drug delivery may itself promote cancer progression by disturbing homeostatic mechanisms of polarity, differentiation, cell fate, and migration [25]. It may rather be easier to intervene pharmacologically via the activation of signaling proteins or enzymes loosely affiliated with the TJ plaque. Feasibility of this approach is demonstrated by the evidence that the activation of calcitonin receptor, which is associated with TJ proteins in prostate cancer cells, disassembles the TJ scaffold and induces invasive phenotype. In contrast, the knock-down of this receptor restores normal TJ function, abolishes invasive characteristics and restores the normal ability of prostate cells to organize acinii in 3D culture [26].

Unfortunately, there are no cancer therapies on the market that specifically target TJs. However, a recent report demonstrates the potential of this approach. A novel, relatively non-toxic anti-cancer molecule extracted from a marine sponge from Red Sea, 4-hydroxyphenylmethylene hydantoin (PMH), prevented TJ disassembly and restored TJ function as assessed by transepithelial electric resistance and paracellular permeability of prostate cancer cells. The compound also reduced orthotopic prostate tumor growth and almost abolished distant metastasis in transgenic mouse model of prostate cancer [27]. These observations support the concept that the restoration of TJ function can attenuate cancer progression and metastasis.

To conclude, the therapeutic modulation of cancer via selective targeting of tight junctions is in its infancy but demonstrates a strong potential. Further investigations into the cell biology of TJs should provide more directions for the development of TJ-targeted therapies for preventing or limiting cancer progression and/or metastasis.

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