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Review

The role of tight junctions in cancer metastasis

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ABSTRACT

Over the last decade, it has become apparent that the tight junction (TJ) is a key component in tumour progression and metastasis. In addition to its role in the control of paracellular diffusion of ions and certain molecules, the TJ has a vital role in maintaining cell to cell adhesion and tissue integrity. Changes in the expression and/or distribution of TJ proteins can result in loss in cohesion of the TJ structure, which in turn results in the ability of cancer cells to become invasive and then ultimately lead to the metastasis of cancer cells. This review will discuss recent insights into how TJ are involved in the process of tumour metastasis.

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1. Introduction

Until recently, cancer research has focused predominantly on tumour development and progression of the tumour at the primary site, despite secondary tumours being responsible for most deaths due to malignancy. However recently, attention has turned towards the field of tumour metastasis [1]. The role of the tight junction (TJ) in tumour metastasis has emerged over the last decade to be one of several new and exciting concepts in understanding the progression and metastasis of human cancer.

1.1. Tight junction structure and function

TJs have a characteristic structure, appearing as discrete sites of fusion between the outer plasma membrane of adjacent cells, appearing as continuous intramembrane particle strands in the protoplasmic face, with complimentary grooves in the extracellular face [2]. These completely circumscribe the apices of the cells as a network of intramembrane fibrils appearing as what is generally described as a series of "kissing" points. The TJ structure is representative of the conglomerate of molecules that constitute, associate with or regulate TJ and since the mid 1980s the list of

Abbreviations: BBB, blood brain barrier; C-CPE, *Clostridium perfringens* enterotoxin; DTA-C-CPE, C-CPE and diphtheria toxin fragment A; EHF, ethyl alcohol extract of *Hizikia fusiforme*; SUR1, sulfonylurea receptor-1; TJ, tight junction; ZO-1, zonula occludens-1.

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molecules has expanded considerably. The molecular components of the TJ have subsequently been investigated extensively [3-6].

Briefly, the TJ consists of three regional components: (1) the integral transmembrane proteins – the TAMP proteins, the claudin family and junctional adhesion molecules (JAM), together with other CTX family members, etc. (2) the peripheral or plaque anchoring proteins, often containing PDZ motifs-zonula occludens (ZO)-1, -2, -3, MAGI-1, etc. (3) TJ-associated/regulatory proteins. The integral transmembrane proteins are the essential adhesion proteins responsible for correct assembly of the TJ structure and controlling TJ functions *via* homotypic and heterotypic interactions. Successful assembly and maintenance of the TJ is accomplished by anchorage of the transmembrane proteins by the peripheral or plaque proteins such as ZO-1 which act as a scaffold to bind the raft of TJ molecules together and provide the link to the actin cytoskeleton and the signalling mechanism of the cell. This is in conjunction with the associated/regulatory proteins.

There are four main functions ascribed to epithelial/endothelial TJ: (1) the sealing of the intercellular space and the separation of apical and basolateral fluid compartments of epithelia and endothelia; (2) acting as a reservoir for TJ molecules to act as intermediates and transducers in cell signalling. *Via* this, the TJ plays a role in the processes of polarity, cell differentiation, cell growth and proliferation; (3) mediators of cell to cell adhesion; (4) as a barrier to cell migration and motility.

Cell adhesion to adjacent cells and the extracellular matrix is key to the organization of epithelium into a tissue. Moreover, cell adhesion is essential for the regulation of cell differentiation, gene expression, motility and growth [7]. These regulatory functions are mediated by cell adhesion molecules, transmembrane receptors and cytoskeletal proteins all of which are organized into multimolecular complexes and the activation of signalling pathways. Whilst the barrier and fence functions of TJ have been well appreciated, it is only relatively recently that concept of the TJ as a complex, multiprotein structure with roles in other cellular processes such as cell polarity, proliferation and differentiation has been recognized [8]. It has become evident that the development of human cancer is frequently associated with the failure of epithelial cells to form TJ and to establish correct apicobasal polarity.

1.2. Tumour metastasis

Tumour metastasis is a series of events that allows the dissemination of tumour cell from the primary site to spread to secondary and tertiary foci. At the time of diagnosis of cancer, at least half of patients already present clinically detectable metastatic disease [9]. Indeed, a higher number of patients will also have micrometastases that would be beyond conventional detection techniques. Therefore, tumour metastasis is the most life threatening event in patients with cancer. The process is composed of a number of sequential events which must be completed in order for the tumour cell to successfully metastasize, the so called metastatic cascade. This process contributes to the complexity of cancer as a multiplex disease. The metastatic cascade can be separated into three main processes: invasion, intravasation and extravasation.

The process of invasion occurs when malignant tumour cells dissociate from the primary tumour mass *via* loss of cell to cell adhesion and invade the surrounding stroma. This involves the secretion of substances to degrade the basement membrane and extracellular matrix and also the expression or suppression of proteins involved in the control of motility and migration. The tumour must also initialize angiogenesis, without which the tumour would fail to develop. Local diffusion for transport of nutrients to and removal of waste products from the tumour site will only suffice for tumours up to 2 mm in diameter [10]. For tumours to grow beyond this limit, a connection must be made to the blood supply. Within the tumours vicinity, blood vessels can provide a route for the detached cancer cells to enter the circulatory system and therefore metastasize to distant secondary and tertiary foci; the process of intravasation [11,12]. Interaction between the stroma surrounding the tumour cell and the tumour cell itself is extremely important in the development of tumour related angiogenesis [13]. The detached cells must then enter the circulatory system and survive the forces involved and the immune system to arrive intact at a distant site. Once the tumour cell has arrived at a likely point of intravasation, it interacts with the endothelial cells by undergoing biochemical interactions (mediated by carbohydrate–carbohydrate locking reactions, which occur weakly but quickly) develop adhesion to the endothelial cells to form stronger bonds, and thus penetrate the endothelium and the basement membrane; the process of extravasation. The new tumour can then proliferate at this focus.

1.3. Tight junctions as barriers to metastasis

The TJ is therefore the first structure impeding the path to successful metastasis of the cancer cells, as TJs exist between the cancer cells themselves and the cells of the endothelium. The TJ structure must be perturbed and disassembled to enable penetration of the cancer cell [14]. TJs of vascular endothelium *in vivo* function as a barrier between blood and tissues against metastatic cancer cells [15]. Since early studies suggested a link between the reduction of TJ and tumour differentiation, experimental evidence has emerged to place TJ in the frontline as the structure that cancer cells must overcome in order to metastasize [16–18]. Following the very early work of Martinez-Paloma and others [19–21] a considerable body of work exists on TJ and their role in a number of diseases. Any changes in cancer cells by up-regulation or down-regulation of relevant TJ proteins results in loss of cell–cell association, cell contact inhibition, leading to uncontrolled growth, loss of adhesion to and degradation of the basemen membrane. Changes in tumour and endothelial cells are also necessary for the successful growth and spread of cancer cells. To facilitate the passage of the cancer cells through this barrier, these must be a concurrent loss of cell–cell association in the endothelium and modulation of the TJ proteins involved. It is patent that changes to the regulation and function of TJ is not just a consequence of cancer progression but is essential to its development and persistence, eventually enabling metastasis and secondary disease. Discovering how TJ are involved in cancer is vital to the effort in understanding and developing diagnostics and treatments for cancer.

This review will discuss the recent insights that have been made in understanding how TJs control the invasion and metastasis of cancer *via* changes barrier function, usually due to changes in TJ protein expression resulting in modifications in the structure of the TJ itself.

2. Tight junctions as controllers of tumour cell invasion during metastasis

The interaction and penetration of endothelium and mesothelium by the metastasizing tumour cell is a key step in the formation of metastasis [22–24]. As our understanding of the molecular structure, mechanism of action and function of the TJ has developed, the TJ can be regarded as a potentially important target for anti-cancer research and a possible area for future therapeutics.

2.1. Tight junction and tumour-endothelial invasion

The regulation of vascular permeability is one of the most important functions of endothelial cells. It has been demonstrated that endothelial cells from different organ sites show different degrees of permeability [25]. Although tumour associated blood vessels

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