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Review Article

Cell-Cell Communications: New Insights in Targeting Tight Junctions through Phytochemicals for Potential Cancer Therapeutic Adjuvants

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ABSTRACT

Cancer is a cellular impairment disorder characterized by the loss of cell cycle regulation leading to aberrant cell proliferation. Cell-cell communication plays a crucial role in cell signaling which is highly disrupted in various malignancies. Tight Junctions (TJs) are major proteins that regulate the proper communication. Dysregulation of TJ proteins make these tumor cells more aggressive leading to tumor invasion and metastasis. Hence targeting TJs might be the novel insights in targeting these highly invasive, metastatic tumors. Due to the prohibitive costs of treatments, side effects and development of resistance, the herbal medications comprising bioactive ingredients became more popular for various human ailments. Unfortunately, the importance of natural compounds has significantly reduced due to the development of modern synthetic techniques to formulate drugs. However, the pharmaceutical industry that adopts chemistry-based drug development in combination with high throughput synthesis has not resulted in expected drug productivity. Hence, focus was shifted back to the natural compounds in search of novel drugs with advanced technology to isolate the biologically active compound from the natural compounds. The current review delivers the importance of TJ regulation, promotion of TJ regulation through phytochemicals for targeting malignant tumor cells.

Keywords: Tumor metastasis; Invasion; Tight junction; Cancer; Phytochemicals

INTRODUCTION

Cellular abnormalities are the root cause of numerous diseases including cancer. Checkpoints of cellular metabolism and genetic aberrations serve as therapeutic targets both in communicable and non-communicable diseases leading to dysregulation in the cell signaling processes. Cell-cell communication is crucial for the tight regulation of homeostasis and hence cells would be connected extracellularly with adjacent cells and intracellularly with various cytoskeletal molecules through cell junctions. These connections provide an integrated, structural diversity across the tissue to regulate the proper functioning of the tissue. Tight junctions, desmosomes, and adheren junctions are the critical players in regulating the normal functioning of cells by providing the cell-cell intimacy. Table 1 describes the various components of cell-cell junctions.

Table 1: Various components associated with cell-cell junctions.

Junctions	Components
Tight Junctions	Occludins, Claudins, Junctional adhesion molecules
Adheren Junctions	Cadherin adhesion receptors, cytoplasmic proteins
Gap Junctions	Connexin transmembrane proteins
Desmosomes	Desmoglein, Desmocollin

Disruption of cell-cell interaction shows a high impact both in cell communication and cell signalling leading to serious health disorders like diabetes, hypertension, inflammation, and even cancer. The Tight Junctions (TJ) present between the adjacent cells, that restrict the paracellular movement of solutes and macromolecules are located near the apex of the lateral plasma membrane in mammals [1]. These are the complex, dynamic

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structures that confine apical connections between epithelial cells [2]. The TJ forms a proteinaceous seal by encircling each cell in order to regulate the diffusion of ions and solutes between the cells which is called the paracellular pathway. The TJ serves as a "fence" and a "gate" simultaneously to maintain segregation of apical and basolateral membrane, and to regulate paracellular pathway respectively. TJ serve a crucial function in cell structure by organising the junctional complex on the apical side of the epithelial cells and also regulate the movement of solutes that pass intercellularly and helps maintain cell polarity [3]. Interestingly, the regions that are present in TJ intracellularly bind to cell signalling molecules and cytoskeleton to regulate cell migration, proliferation, and differentiation [4].

Disruption in cell communication results in accumulation of cells accompanied with poor/absence of apoptosis which is the characteristic feature of various malignant cells [5,6]. Tumor cells invade various tissues and organs accompanied by disruption of TJs. This is because the disrupted TJ elevates the production of Matrix Metalloproteinase (MMPs) that aids in transformation of epithelial cells to mesenchymal cells which is one of the hallmarks of tumor metastasis [7]. The present review focusses on the crucial role played by tight junctions in cancer and might give new insights targeting the cell-cell communications in drug-resistant cancers using phytochemicals as adjuvants.

STRUCTURE OF TIGHT JUNCTIONS

TJs serve as a stopper between the epithelial and endothelial monolayers thereby serving as gate keepers to allow the passage of small molecules and ions [8]. Followed by other cell-cell junctions TJ is localized at the apical lateral side of the epithelial tissue, while in endothelial cells these TJs are localized at the apical basal side. TJ is formed by the organisation of multiprotein complexes that involves both transmembrane proteins and cytoplasmic proteins [9].

Proteins involved in tight junction

Previous studies demonstrated that TJ molecules activate various signalling pathways in cancer. To summarise, epithelial/endothelial TJ is thought to serve following purposes. Firstly, TJ molecules are intended to separate the apical and basolateral fluid compartments of epithelia and endothelia accompanied with sealing intercellular space. Secondly, it serves as a mediator of cell-cell contact there by regulating cell polarity, differentiation, growth, and proliferation by serving as intermediates and transducers in cell signalling. Finally, they act as barrier to cell migration and motility. Claudin and occludin are the two major transmembrane protein families of tight junctions that usually exist as homodimers viz., claudin-claudin and occludin-occludin complexes between cells. Other protein families of TJ include Junctional Adhesion Molecules (JAMs), and cytoplasmic zonula occludins designated as ZO-1, ZO-2, and ZO-3. JAMs are type-1 proteins that comprises ectodomains that are similar to those found in immunoglobulin domains. Claudins are expressed in human small intestine and in epidermis in various isoforms. Cluadin-1,2,3,4,5,8,12 and 15 are expressed in human small intestine while claudin 1,4, and 7 are expressed in epidermis. Various studies demonstrated that the dysregulation of TJ proteins is associated with various diseases.

FUNCTION OF TIGHT JUNCTIONS

The intestinal epithelium plays a major role in digesting the ingested food and to absorb, circulate the absorbed nutrients and dietary factors. To maintain these functions the intestinal epithelial should interact with several barrier components, and intercellular TJs are one among them. When the barrier integrity is disrupted, immune cells are robustly activated leading to chronic inflammation of the gastrointestinal tissues. Disruption of the barrier integrity leads to the passage of inflammatory cytokines to various organs *via* circulation resulting in the pathogenesis of various non-intestinal disorders. Spontaneous opening and closing of TJ is a dynamic process that contributes to the modulation of tissue permeability with respect to the variations in the chemical constituents such as type and concentration of proteolytic enzymes, ionic content, and solute, the gut microbiota composition, etc. However, vesicular trafficking of TJ proteins between the cell membrane and cytosol might lead to TJ protein destruction. Destruction of TJ proteins by vesicular trafficking might be regulated by various exogenous factors and physiological modulators [10].

TJ act as a battleground to maintain the barrier integrity of the intestinal epithelium. The opening and closing of TJs are highly regulated. The TJ present between the adherent cells is located near the apex of the lateral plasma membrane in mammals. These are the complex, dynamic structures that confine apical connections between epithelial cells [11]. The TJ forms a proteinaceous seal by encircling each cell in order to regulate the diffusion of ions and solutes between the cells which is called the paracellular pathway. The TJ serves as a "fence" and a "gate" simultaneously to maintain segregation of apical and basolateral membrane, and to regulate paracellular pathway respectively. TJ serve a crucial function in cell structure by organising the junctional complex on the apical side of the epithelial cells. They regulate the movement of solutes that pass intercellularly and maintain the cell polarity. Interestingly, the regions that are present in TJ intracellularly bind to cell signalling molecules and cytoskeleton to regulate cell migration, proliferation, and differentiation [12].

DISRUPTION OF TIGHT JUNCTIONS

Defending the body from stress stimuli caused by inflammation and infection relies heavily on TJs of the intestinal epithelial barrier. TJ homeostasis alteration is thought to induce pathogenesis of various disease especially cancer as TJs is majorly involved in cell-cell interactions and cell signalling. Alteration in TJ homeostasis is influenced by factors such as proinflammatory cytokines, pathogenic bacteria, and Lipopolysaccharides (LPS) [13].

Proinflammatory Cytokines

Proinflammatory cytokines like TNF-α, IL-1, and IFN promote permeability of TJ. It is been demonstrated that both IL-1β and TNF-α are involved in suppressing TJ barrier function by activating NF-κB with simultaneous decrease in ZO-1 protein level [14]. Alternatively, blocking of NF-κB prevents TNF-α induced TJ barrier opening and ZO-1 downregulation. Interestingly, IL-1β treatment with Caco-2 cell monolayers suppressed occludin protein level but did not affect ZO-1 protein level [15].

Pathogenic bacteria and lipopolysaccharides

Toxins and pathogenic bacteria play a crucial role in maintaining the endothelial barrier. For instance, the intestinal epithelial TJ barrier is altered by certain enteric pathogenic bacteria such as *E. coli* and S. *typhi* leads to intestinal inflammation [16]. On the other hand, LPS a crucial cell wall component of various gram-negative bacteria contributes to a leaky small intestine ultimately resulting in TJ protein assembly modification. Apart from altering TJ protein assembly, LPS also leads to altered expression of occludin and ZO-1 by inducing systemic inflammation [17]. Hence, the TJs are to be regulated properly for the better functioning and delivering of therapeutic agents.

ROLE OF TJs IN PATHOPHYSIOLOGY OF VARIOUS MALIGNANCIES

Tissue organization is characterised by the capability of epithelial cells to adhere with one another and with the extra cellular matrix. Cell adhesion apart from tissue organization is essential for regulating cell differentiation, gene expression, motility, and cell growth [18,19]. These regulatory functions are mediated by activating signalling pathways through the formation of multimolecular complexes *via* cell adhesion molecules, transmembrane receptors, and cytoskeletal proteins. Evidence from recent studies demonstrates that the failure of epithelial cells to organize into TJ and establish perfect apicobasal polarity is often implicated in development of various chronic diseases including cancer.

Tumor metastasis is one of the major hallmarks of cancer progression and is often associated with invasion of malignant tumor cells, which is associated with the dissociation of cancer cells from the primary tumor mass [20-22]. Unfortunately, the invasion is characterized by loss of cell-cell adhesion resulting in invade of surrounding stroma. The key step in metastasis initiation would be the interaction and penetration in the metastasising tumor cell of the endothelium and the mesothelium. Therefore, it could be demonstrated that during metastasis TJs act as controllers that regulate tumor cell invasion. Figure 1 describes the mechanism of tumor invasion through TJ disruption [23]. Studies showed that mutations in oncogenes which results in hyper activation of the particular gene is positively correlated with increased leakiness of TJs in cancer suggesting that increased permeability of epithelium is associated with decreased epithelium barrier function leading to tumor development. Interestingly, Mullin, et al. hypothesised that in epithelial carcinogenesis TJ leakiness is the late event that would be occurred [24].

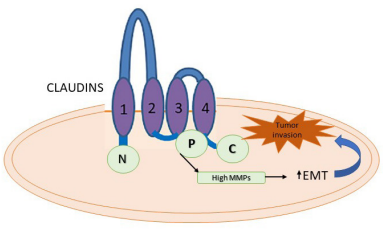

Figure 1: Impact of TJ disruption on tumor invasion and metastasis. Claudins are the group of TJ proteins that play a critical role in tumor invasion, migration, and metastasis. Activation of claudins by phosphorylation induces synthesis of bulk quantities of Matrix Matallo Proteinase (MMPs) which aids in tumor cell invasion by enhancing Epithelial Mesenchymal Transition (EMT).

Additionally, claudin-2 which is member of TJ protein family has been implicated in many proliferative pathways that often dysregulated in various diseases including cancer. Interestingly, many studies have demonstrated a positive correlation between altered claudin-2 expressions with respect to cell proliferation [25]. It has been suggested that claudin-2 might be a pro-proliferative factor that acts as a pro-proliferative signalling pathway. On the other hand, *CDKN1B* a cell cycle regulator whose expression is high in quiescent cells is also interrupted by the claudin-2 which results in blocking the cell to enter the cell cycle [26]. Since *CDKN1B* is a tumor suppressor which suppressor the tumor growth by blocking the cell entry, the altered claudin-2 expression negatively regulates the expression of *CDKN1B* gene [27]. On the other hand, JAMs a multifunctional transmembrane TJ protein belonging to immunoglobulin superfamily inhibited apoptosis in gastric cancer with simultaneous proliferation of actively dividing cancer cells [28]. Surprisingly, inhibition of occludins an integral membrane protein localized in TJ has been implicated to inhibit apoptosis suggesting that occludin plays a crucial role in cell death signalling [29].

Over past few decades, numerous studies have shown that the aberrant TJ function and expression in cancer progression suggests that TJ components offer intriguing and novel targets for cancer diagnosis, detection, and therapy resulting to an innovative therapeutic approach to treat cancer [30]. Most of the commercially available antineoplastic drugs target DNA disruption with the help of topoisomerase inhibitors. Although research has been improved splendidly that target TJ components confer high invasive potential and drug resistance [31]. Therefore, targeting TJ signalling with the help of natural components has been shown more interest.

ROLE OF NATURAL COMPOUNDS IN PROPER REGULATION OF TIGHT JUNCTIONS

Administration of drugs is compulsory when a person suffers from acute or chronic disease. Unfortunately, injections show a drastic impact on patient's quality of life [32]. There are other ways such as nasal, oral, pulmonary routes but encounter several obstacles. Among those obstacles, movement of hydrophilic macromolecular drugs across the epithelia is the major concern. The small intestine which absorbs the dietary nutrients is restricted to absorb the chemotherapeutic drugs is due to the presence of TJs formed by the adjacent epithelial cells forming a biological barrier. Research has been shifted towards the therapeutic efficacy of various natural compounds in regulating TJs leading to novel cancer therapeutic approaches [33].

Quercetin

Quercetin, a flavonoid is a class of secondary metabolite found in various plants has various biological properties such as anticarcinogenic, anti-inflammatory, antiviral, antioxidant, etc. [34]. Quercetin, that comes under flavonoids have been shown to regulate tight junctions because of their potent roles in various health ailments [35]. It is well known that tight junctions play a crucial role in maintaining cell-cell communication and regulates the flow of small molecules and ions. In diabetic patients, there is a high risk of attaining cerebrovascular complications [36]. The reason behind this is hyperglycemia which is the hallmark of diabetes alters the cerebral endothelial cellular function that are interconnected with tight junctions. They comprise three transmembrane proteins called occludins, claudins, and Junctional

Adhesion Molecules (JAMs). Surprisingly, hyperglycemia also shown to regulate occludin, claudin, ZO-1 and ZO-2, and tight junction protein synthesis negatively. Interestingly, NF-κB is also associated with the production of cell adhesion molecule and hence hyperglycemia induced inflammation is associated with over production of these cell adhesion molecules resulting in promotion of adherence and trans endothelial migration [37].

Due to their antioxidant potency and ability to inhibit wide range of kinases including kinases involved in cancer cell growth, proliferation, and metastasis, quercetin is a potent molecule to induce cancer cell death by generating oxidative stress. Studies showed that in ascites cells of Dalton lymphoma carrying rats' quercetin has induced receptor mediated apoptosis. Additionally, Maurya A.K and co-workers proved that quercetin is capable to inhibit protein kinase C activity which is a key player in regulating cancer progression.

The role of quercetin in TJ integrity has been investigated in various studies. In the absence of pro inflammatory cytokines quercetin has been reported to improve TJ barrier function in Caco-2 cell lines. Surprisingly, there was a significant increase in the expression of claudin-4 when Caco-2 cells were treated with 200 μM quercetin for 24 hours. Unfortunately, there is no significant elevation of other TJ proteins such as occludins, claudin-1, claudin-3, and claudin-7. Interestingly, administration of quercetin elevated the Transepithelial Electrical Resistance (TER) while suppressing the paracellular marker lucifer yellow flux. TER could be defined as the measurable unit that detects the capacity of TJ to regulate the flow of ions and small molecules through para cellular pathway. Therefore, elevation of TER indicates the logarithmic increase in TJ function to permit the passage of small molecules and ions. In order to assess the beneficial role of quercetin on TJ cellular mechanisms, several protein kinase inhibitors were used. Among all the protein kinase inhibitors used staurosporine, and H7 demonstrated quercetin's protective role in regulating TJ barrier. Interestingly, it has been demonstrated that 100 μM concentration of quercetin has enhanced the TJ integrity by diminishing PKC through subsequent modulation of various TJ-related proteins including claudins, occludins, and zonal occludins by suppressing PKC. All these results show that quercetin mediates TJ barrier integrity by suppressing various protein kinases.

Berberine

Berberine comes under the group of isoquinoline alkaloids. It is a quaternary ammonium salt enriched in roots, rhizomes, and stem bark of numerous plants under Berberis genera. The protective role of berberine has been investigated in the mouse model comprising endotoxinemia, the study showed that intragastric pre-treatment with berberine partially prohibited the ultrastructural damage of TJ by reversing the LPS-facilitated redistribution of occludin, ZO-1, claudin-1, claudin-4 in colon epithelium. Interestingly, when the rats with type-2 diabetes were pre-treated with berberine for 9 weeks significantly enriched the disruption of intestinal permeability, pro-inflammatory intestinal fluctuations. L, Gu et al. have demonstrated that berberine is non-toxic to human epithelial cells and is shown to tighten TJ barrier. Interestingly, a study conducted by Ma et al. TJ permeability is regulated by NF-κB whose activation is negatively regulated by berberine. Surprisingly, berberine which positively correlates with TJ integrity was not able to induce sub cellular localization of occludin which is a major component of TJ and key regulator of TJ barrier function even at high doses [38]. Furthermore, berberine has shown to diminish pro-inflammatory cytokine-induced increase in intestinal epithelial TJ permeability [39].

Interestingly, in endotoxemic mice administration of berberine partially attenuated intestinal epithelial TJ barrier dysfunction. When distal ileum and colon were subjected to IHC the results demonstrated that berberine improves morphological changes facilitated by LPS. A study conducted by Qiuke Hou et al., suggested that berberine modulates epithelial TJs by restoring the damage caused to the structural integrity of colon epithelium, downregulating NF-κB, Myosin Light Chain Kinase (MLCK) which facilitate cell movement and migration by modulating membrane tension, Tumor necrosis factor receptor associated factor (TRAF) which mediates signal transduction expression with simultaneous upregulation of occludin, claudin, and ZO-1 expression [40]. On the other hand, TJ dysfunction contributing to diarrhoea and inflammatory bowel disease is mediated by TNF-α. TNF-α does this by suppressing claudin-1 expression while elevating claudin-2 levels. However, the TNF-α mediated claudin dysregulation was reversed by berberine. All these data suggest that berberine plays a crucial role in suppressing carcinogenesis mediated by TNF-α which is considered as one of the major regulator of cancer cell proliferation.

Also, because of their ability to interact with nucleic acids berberine is considered to possess potent antineoplastic properties. It is well known that topoisomerase inhibitors are the potent anticancer drugs that are being approved and used clinically. Interestingly, berberine has showed its potentiality to inhibit topoisomerases as well as telomerases by specifically binding and stabilizing DNA triplexes finally accounting for their antiproliferative properties. Furthermore, when berberine was administrated in the human A549 lung cancer cell lines resulted in modification of microtubule-associated protein-1 light chain-3 (LC-3) accompanied with tumor shrinkage in mice model [41,42]. Studies showed that berberine in combination with cisplatin and evodiamine elevated the cytotoxic effects of the anti-cancer drugs and resulted in cancer cell death in various cancers [43].

Genistein

Genistein chemically regarded as 4', 5, 7 trihydroxy isoflavone is one of the major constituents of soybean. Genistein resembles human estrogen stereo-chemically and has a diphenol structure Genistein plays a vital role in numerous biological pathways by targeting various molecules such as protein tyrosine kinases, topoisomerases, ABC transporters, etc which are the sole mediators for tumor invasion, proliferation, and drug-resistance [44]. With the discovery of estrogenic properties genistein became one of the major interests as a potential drug supplement for treating various diseases such as obesity, osteoporosis, metabolic syndromes, cancer, etc.

It is a well-known fact that phosphorylation of TJ proteins is associated with TJ structure and function and genistein has been reported in numerous studies to regulate TJ proteins and its integrity. Surprisingly, the TJ barriers would be opened when the intestinal cells interact with enteric bacteria such as *E. coli* and *S. typhimurium*. However, administration of 300 μM genistein blocked the invasion of enteric bacteria by preventing TJ barrier opening. Another study demonstrated that genistein enhanced TJ barrier dysfunction induced by oxidative stress associated with occludin phosphorylation suppression. *In vitro* studies support the effectiveness of genistein which induces oxidative stress as a potent

chemotherapeutic agent against liver cancer. As a result of its potent activity on apoptosis and cell cycle regulation genistein has shown to be promising approach to affect the hepatocellular carcinoma. By downregulating Matrix Metalloproteinase 9 (MMP-9), Epidermal Growth Factor Receptor (EGFR), and consequent suppression of NF-κB genistein promotes anti-invasive and anti-metastatic properties. Interestingly, genistein inhibited cell proliferation and induced apoptosis in the human gastric cancer cell line BGC-823 in a dose-dependent and time-dependent manner. Additionally, genistein targets and attenuates PI3K/Akt pathway resulting suppression of colon cancer growth and proliferation.

Capsaicin

Capsaicin chemically referred as trans-8-methyl-N-vanillyl-6-nonenamide is a naturally occurring bioactive ingredient found in hot chilli peppers of the genus *Capsicum*. Because of the presence of vanillyl group the capsaicin is considered as vanilloid a proto-alkaloid with nitrogen located in the side chain. The role of capsaicin in TJ permeability has been extensively studied on $CaCo_2$ a human colon cancer derived epithelial cell line, widely used as intestinal epithelial model. Studies demonstrate the effect of capsaicin on TJ permeability in $CaCo_2$ cell lines. Interestingly, studies have demonstrated that cofilin; a family of actin-binding proteins is associated with TJ opening when dephosphorylated. However, opening of TJ was induced in capsaicin treated $CaCo_2$ cell lines associated with dephosphorylation of cofilin. Additionally, capsaicin treatment also altered F-actin structure associated with TJ protein localization [45]. However, Tomoko Shiobara et al. showed that exposure of $CaCo_2$ cells with capsaicin resulted in significant decrease in occludin amount but there was no change in TJ protein localization. The results from their study suggested that TJ opening could be mediated by two mechanisms which could be the subcellular actin distribution associated with modulations in the polymerisation of actin filaments and the other possible mechanism could be reduction in the TJ occludin concentration. Finally, they confirmed that capsaicin induced occludin down regulation coupled with actin alteration affects the TJ integrity resulting to TJ opening in dose-dependent manner. Interestingly all these studies concluded that capsaicin induces TJ barrier opening in various mechanisms [46].

Recent studies have implicated the role of capsaicin in inhibiting tumor progression and inducing tumor cell death. It is very interesting that capsaicin has the ability to restrict the progression of tumor cells without inducing its cytotoxicity effects on normal healthy cells. Capsaicin was proposed to be a novel therapeutic agent for cancer therapy as it would not affect the normal cells while effectively killing the tumor cells [47]. However, the role of capsaicin in anti-cancer activity was still in debate as it plays a dual role serving as a carcinogen as well as cancer preventing agent. Interestingly majority of the studies showed the anti-tumor potentiality of capsaicin rather than its tumorigenicity capacity [48].

DISCUSSION AND CONCLUSION

TJ regulates the paracellular transport of various substances such as ions and small molecules through the intestinal epithelium and is associated with the physical barrier function allowing the passage of essential ions and small molecules. This is aided by the presence of intracellular space in the plasma membrane of adjacent cells. Numerous studies have been done to reveal the role of TJ permeability in pathogenesis of chronic diseases and suggested that TJ dysfunction is associated with inflammatory and metabolic diseases. Hence maintaining proper TJ integrity is likely to be effective strategy to yield better cancer prognosis. Phytochemicals are coming into the light of research due to the presence of numerous active ingredients that are capable of fighting against various diseases including cancer through modulating TJ integrity. However, these plant derived bioactive compounds such as quercetin, berberine, genistein, capsaicin, curcumin, and many more natural compounds have been shown to be effective in enhancing the TJ integrity *via* TJ proteins and inflammatory signalling pathways, further molecular studies are needed to confirm the effectiveness of natural compounds on TJ permeability and integrity which might lead to the development of preventive medicine and therapeutic agents against these chronic diseases.

AUTHOR CONTRIBUTIONS

Wrote the manuscript: PC and SLP; figures and tables: JANM; data compiling: GJM and SNSL; Conceptualized the study: SLP. Overall supervision of the study: SLP

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