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Review

Claudin-1 role in colon cancer: An update and a review

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Summary. Tight junction proteins are essential for sealing the cellular sheets and controlling para-cellular ion flux. Our understanding of the role that tight junction proteins, particularly claudins, play in cellular functions and pathologic conditions is continuously expanding. Particularly, the role of claudin-1 in oncogenesis in multiple locations in the human body is coming to light. This review will shed light on the role of claudin-1 in colon cancer. It will address the mechanisms through which claudin-1 becomes dysregulated in colon cancer. This will provide a platform to address results of claudin-1 expression in the third most common malignant tumour worldwide. Furthermore, it will provide updates about possible use of this biomarker in the surveillance of difficult colon maladies, such as inflammatory bowel disease. The use of claudin-1 as a biomarker of diagnostic and prognostic values will provide Medicine with much needed ammunition in the fight against cancer and will bring about, with added refinements, a new chapter in the era of personalized medicine to tackle this disease and match its destructive course with equally powerful and specifically targeted therapies.

Key words: Colorectal cancer, Tight junction, Oncogenesis, Metastases, Claudin

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Introduction and background

Claudins

Tight junctions such as claudin proteins along with adherens junctions and desmosomes form the backbone of cellular sheets. Tight junctions control paracellular ion flux. In addition, they also play critical roles in maintaining cell polarity and signal transductions (Tsukita and Furuse, 2000; van Itallie et al., 2006). The claudins are a family of at least 29 closely related transmembrane proteins, most of them are well defined at the genomic and proteomic levels. Claudins are found in a variety of normal tissue, hyperplastic tissues, benign and malignant neoplasms. Several types of claudins may be found in one normal tissue. Claudins are present on the most apical, lateral aspect of the cell membrane. A cell may express one, two or more types of claudin proteins. The claudin protein extends two loops to the nearby extracellular matrix (ECM) which interact with same or other claudins in nearby cells, respectively.

Loss of epithelial integrity of cellular sheets, accompanying alterations in claudins' levels, with resultant increased para-cellular influx play a critical role in providing a space for the movement of tumor cells, and act as a conduit of nutrients for tumour cells lurking under the epithelial surface.

Several studies have pointed out that in cancer, claudins exhibit changing levels, with some showing increased, while others showing decreased expression levels (Dhawan et al., 2005; Oku et al., 2006; Dos Reis et al., 2008; Ouban and Ahmed, 2010; Ouban et al., 2012). Furthermore, manipulation of claudin levels in-vitro and animal studies (Dhawan et al., 2005; Oku et al., 2006; Dos Reis et al., 2008) resulted in regression of

aggressive tumor traits, especially cell motility, invasion and metastases. This could have great potential in the fight against cancer and its complications, especially invasion and metastases. Among this group of proteins, claudin-1 stands out as the most promising. It has shown utility, both diagnostically and prognostically, in many types of human cancers, including oral, gastric, liver and colon cancers (Oku et al., 2006; Dos Reis et al., 2008; Ouban and Ahmed, 2010).

Colon cancer

Globally, colorectal cancer (CRC) is currently the second most common cancer in women and the third most common in men, with 1.4 million new cases annually (Ferlay et al., 2012). The global burden of colorectal cancer (CRC) is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030. (Arnold et al., 2017) Generally, CRC incidence and mortality rates are still rising rapidly in many low-income and middle income countries; stabilising or decreasing trends tend to be seen in highly developed countries where rates remain among the highest in the world (Arnold et al., 2017).

Claudin-1 in colon cancer

Claudin-1's expression in colon cancer is complex. While most of the studies performed to analyse expression of claudin-1 in colon cancer and the role this protein plays in tumour development have shown binary mode between low and high expression, one particular study has shown that through hierarchical cluster analysis, three patterns of claudin-1 immunoreactivity could be discerned separating colon cancer patients into good, intermediate, and poor prognostic groups; with different phenotypes and independent survival outcomes using multivariate regression analyses. The group expressing the highest claudin expression in this cohort was shown to have the best prognosis among all patients (Matsuoka et al., 2011). In another study, it was interesting to note that while claudin-1 expression significantly correlated with tumour invasion, the same study (Nakagawa et al., 2011) showed that overall survival rate was significantly higher in patients in the claudin-1 high expression group than in the low group. Furthermore the disease-free survival rate after curative surgery was higher in the claudin-1 high expression group than in the low one (Nakagawa et al., 2011). The authors, using univariate and multivariate analyses of expression levels of claudin-1, indicated that this expression is significantly correlated with overall survival and that high expression is an independent predictor of overall survival.

In addition, some expression levels studies have pointed conflicting results (Ersoz et al., 2011). Suppressed claudin-1 expression in colon cancer was reported in several studies and was linked with depth of invasion, higher histological grade and lymph-vascular/perineural invasion (Resnick et al., 2005; Abdelzaher et al., 2011; Yoshida et al., 2011; Shibutani et al., 2013; Suren et al., 2014). Resnick et al. 2005 went further to affirm that loss of claudin-1 expression is a strong predictor of disease recurrence, and poor patient survival in stage II colon cancer. Other studies on the other hand, have shown increased expression of claudin-1 in CRC cells (Miwa et al., 2001; Dhawan et al., 2005; Grone et al., 2007; Huo et al., 2009; Tang et al., 2011) resulting in increased depth of tumor invasion (Dhawan et al., 2005; Huo et al., 2009) through activation of the matrix metalloproteinases (Takehara et al., 2009). In 2010, the author of this review published an overall review of the roles of claudins in cancer, including colorectal cancer. A brief review of claudin-1's role in colorectal cancer was mentioned in that article (Ouban and Ahmed, 2010).

More attention is paid to the role claudin-1 plays in colorectal cancer development. Recently some of the studies assessing that role showed a stepwise increase (a dose effect) in this expression. For example, Claudin-1 expression was significantly higher in colonic adenomas and adenocarcinomas compared to normal colonic mucosa. Furthermore, it was shown that this expression moves from the normal position of membranous to becoming cytoplasmic in both adenomas and adenocarcinoma (Bezdekova et al., 2012). The same study noted that the cytoplasmic localization, when present in colon cancer, increased likelihood of epithelial-mesenchymal transition and higher metastatic potential.

Furthermore, other studies started painting a different picture regarding claudin-1 role in colon cancer. For example, Matsuka et al. showed that the central regions of the colorectal tumours retained the claudin-1 expression while the invasive edges of tumours have lost this expression. Those tumours which experienced this peripheral loss of claudin-1 were more likely be poorly-differentiated colorectal cancers (Matsuka et al., 2011). This may suggest that the role of claudin-1 may be that of a promoter of tumorigenesis, and once the tumour is established and its cells start the invasion process, the expression of this protein will be lost in tumour cells.

Not only was decreased expression of claudin-1 associated with poor differentiation of colorectal tumours but also with lympho-vascular and peri-neural invasion in patients with stage II and III rectal adenocarcinoma (Yoshida et al., 2011). This study established claudin-1 as a strong predictor of disease recurrence and poor survival in stage II and III rectal cancer patients.

When it comes to colorectal cancer metastases, Kinugasa et al. found that claudin-1 expression was increased in both primary colonic tumors and its related hepatic metastases. The expression in both the primary tumors and its relevant hepatic metastases was more pronounced than normal colonic mucosa. Claudin-1 expression was also found in the cytoplasms of these

colorectal cancer cells, both in the original tumours and the metastases (Kinugasa et al., 2012). Claudin-1 expression in the above mentioned cells mirrored that of beta-catenin. This has been reported previously by Miwa et al. (2001) where Claudin-1 is evidently one of the genes strongly related to B-catenin, which is known for mediating the oncogenic Wnt/beta-catenin transduction pathway.

Mechanisms of claudin-1 expression in colorectal cancer

Since the beginning, several studies have attempted to offer putative mechanisms of claudin-1 in colorectal cancer. Fig. 1 depicts how claudin-1 may affect colonic carcinogenesis.

The first such study pointed out the role of claudin-1 in activation of Transcription Factors present in the colonic epithelium resulting in tumor development (Bhat et al., 2012). Cdx-2, a member of the caudal home-box gene family (Duprey et al., 1988; James et al., 1994; Charite et al., 1998), regulates claudin-1 expression in the intestinal mucosa. It does that along with Cd-x1, a member of the same family of genes, and GATA4, a known transcription factor involved in the regulation of proliferation and differentiation of intestinal epithelial cells. According to this study, transfection of Cd-x2 into the SW 480 colon cancer cell lines resulted in a significant increase in the expression of claudin-1 in those cells. The authors (Bhat et al., 2012) also validated the above results by immunohistochemistry, where claudin-1 immunostaining mirrors that of Cd-x2 in both the cytoplasms and nuclei of the colorectal cancer cells $P<0.01$ in a series of fifty primary and metastatic colorectal cancers.

Anoikis was also analysed as a possible pathway through which Claudin-1 may induce colorectal carcinogenesis, and coming from the same center as the study above (Singh et al., 2012), which analysed colorectal carcinogenesis and its relationship to claudin-1 associated resistance to anoikis. The anoikis resistance in colorectal cancer is rendered through the partnering of claudin-1 with Src/p Src in colon cancer cells. Src-tyrosine kinase is known to promote cell proliferation and resistance to anoikis (Wei et al., 2004; Reginato et al., 2005; Yamaguchi et al., 2008). The authors of this study (Singh et al., 2012) have shown that resistance to anoikis mediated by Src-pSrc possibly happens through multiple, down-stream targets, including the Bcl-2, a gene known to be master regulator of apoptosis. While the authors of this study (Singh et al., 2012) have found no changes in Bcl-XL levels upon modulation of claudin-1 or Src/p-Src levels, there was marked over-expression of Bcl-2 levels in cancer cells that expressed high levels of claudin-1 and were resistant to anoikis compared with low claudin-1 expressing cells. To further prove the above, when an inhibitor to the phosphorylation and activation of Src/p-Src was introduced in colorectal cancer cells expressing claudin-1 in the above study, not only was claudin-1-dependent resistance to anoikis inhibited; but Bcl-2 expression was also suppressed. The above may provide an explanation for how claudin-1 makes colon cancer cell lines resistant to anoikis, thus favouring tumour cell survival and progression. Immunoprecipitation experiments by the authors of this study (Singh et al., 2012) confirmed the presence of the activated form of Src protein in claudin-1 pull down and the presence of Src and claudin-1 in ZO-1 pull downs, and vice versa. Taken together, the above suggests the formation of a multiprotein complex composed of activated form of Src, ZO-1 and claudin-1 (Singh et al., 2012).

A third possible way through which Claudin-1 may

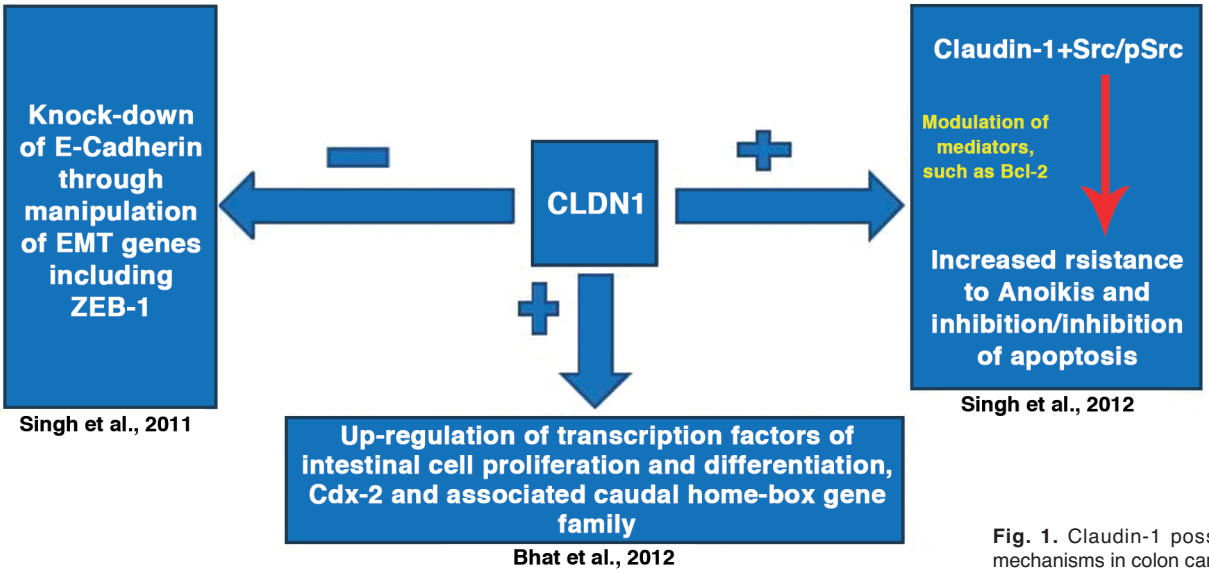

Fig. 1. Claudin-1 possible etiologic mechanisms in colon carcinogenesis.

induce and promote colorectal oncogenesis is through modulating cell adhesion (Singh et al., 2011). This happens through weakening the integrity of the cellular adherent and tight junctional seals. By decreasing the expression of E-cadherin through increasing the expression of ZEB-1 gene claudin-1 over-expression will ensure that cellular seals are weakened. These seals protect the layers beneath from toxins and carcinogens (Singh et al., 2011). This will give the cells underneath ample time and space to get exposed to all the toxins carried in the gastrointestinal tract.

Claudin-1 expression in ulcerative colitis and colorectal cancer and the beta-catenin pathway

Several studies (Weber et al., 2008; Mees et al., 2009; Kinugasa et al., 2010) have shown that increased, non-remittent inflammatory activity, the likes of which is seen in ulcerative colitis, results in high grade dysplasia and in up-regulation of beta-catenin transcriptional activity. It was shown that this increased activity in the nuclear transcriptional factor is mirrored by increased activity of claudin-1 in the colonic mucosal epithelium. The studies above have shown that beta-catenin upregulation happens first, in the early stages of the increased inflammatory activity of ulcerative colitis, followed by increased expression of Claudin-1 towards the late stages of the disease when high-grade dysplasia sets-in. Bhat et al. (2016) have shown that this increased expression of claudin-1 in the course of colitis may be happening through the TNF-α. This pro-inflammatory cytokine induces epithelial to mesenchymal transition (EMT) phenomenon through modulation of claudin-1. It is interesting to note that TNF-α treated colorectal cancer cells showed increased expression of Src (Bhat et al., 2016). This may link TNF- α to claudin-1 to increased resistance of anoikis as mentioned previously in this article (Singh et al., 2012).

Table 1. Claudin-1 levels in colorectal cancer studies and its role in oncogenesis.

	Decreased expression correlating with poor prognosis, increased invasive and metastatic abilities	Increased expression correlating with poor prognosis, increased invasive and metastatic abilities
Matsuoka et al., 2011	Best Prognosis with Highest Expression	
Nakagawa et al., 2011		Increased expression results in increased depth of invasion. Also overall survival was best in the highest expression group
Suren et al., 2014	Decreased expression correlated with aggressive behavior	
Shibutani et al., 2013	Low expression of Claudin-1 correlates well with poor prognosis in colorectal cancer	
Abdelzaher et al., 2011	Decreased expression of claudin-1 correlated with poor prognosis	
Yoshida et al., 2011	Decreased expression of claudin-1 in rectal cancer is factor for recurrence and poor prognosis	
Resnick et al., 2005	Loss of claudin-1 is a strong predictor of disease recurrence and poor patient survival in stage II colon cancer	
Dhawan et al., 2005		Claudin-1 overexpression in colon cancer results in increased invasive and metastatic abilities
Miwa et al., 2001		Claudin-1 overexpression may play a role in colorectal tumorigenesis
Tang et al., 2011		Claudin-1 was over-expressed at both the mRNA and proteins levels in colorectal cancerous tissues compared to adjacent normal mucosa
Huo et al., 2009		mRNA levels of claudin-1 is well correlated with colon cancer invasive depth levels. Increased expression of claudin-1 resulted in increased aggressive behavior of tumor cells
Grone et al., 2007		mRNA and protein levels of claudin-1 were upregulated in colorectal cancer cells and appear to play a role in its tumorigenesis
Bezdekova et al., 2012		Claudin-1 expression in colonic adenomas and adenocarcinomas was higher than normal adjacent mucosa and contributed to EMT phenomenon and higher metastatic potential in colorectal cancer cells
Kinugasa et al., 2012		Increased expression in colorectal cancer and its hepatic metastases
Bhat et al., 2012		Increased expression of claudin-1 upregulates Cdx-2 resulting in increasing proliferation and dedifferentiating of colonic mucosal cells
Singh et al., 2012		Increased expression of claudin-1 in colon cancer cells results in increased resistance to anoikis and inhibition of apoptosis
Singh et al., 2011		Increased expression of claudin-1 upregulates ZEB-1 in colon cancer cells resulting in epithelial mesenchymal transition phenomenon and increased invasive abilities
Kinugasa et al., 2010		Upregulation of nuclear transcription B-catenin is related to claudin-1 upregulation and will result in EMT in colon cancer cells expressing the two above listed genes

Because of the difficulty in surveying UC patients for CRC and as a result of the finding from the above studies, claudin-1 up-regulation may be considered as an early marker of oncogenic transformation in the setting of inflammatory bowel disease.

Conclusion

It is clear from the above that claudin-1 plays a significant role in the initiation and progression of colorectal cancer. For this tight junction protein to receive its full potential, certain refinements should be attempted. Table 1 lists the studies that have analysed the role of claudin-1 in colorectal cancer and reported on the expression level of this biomarker and its relevance to prognosis. As can be seen from Table 1, some studies have shown that claudin-1 is over-expressed in colorectal cancer and this over-expression has a good prognostic value, overall survival, disease-free survival, less metastases and less aggressive disease.

However, it is important to mention that there are other studies that point in a completely opposite direction. Dhawan et al. (2005) and Huo et al. (2009) have pointed out that over-expression of claudin-1 in colorectal cancer is linked with increased depth of invasion through activation of the MMPs (Takehara et al., 2009) as could be seen in Table 1.

Many explanations could be offered to these seemingly contradictory results. One explanation in particular, is that colorectal cancer is not caused by a single mechanism, rather several mechanisms are operating in colorectal cancer, which may or may not converge on the tight junction proteins, altering its expression levels. None of the studies above have addressed this part of the story of claudin-1 and colorectal cancer. In short, it is now known that CRCs can arise from one or a combination of three different mechanisms, namely chromosomal instability (CIN) (Fearon and Vogelstein, 1990), CpG island methylator phenotype (CIMP) (Weisenberger et al., 2006), and microsatellite instability (MSI) (Sameer et al., 2014). Each one of those pathways has its own set of deregulated genes, for example, the classical CIN pathway has mutations in adenomatous polyposis coli (APC), KRAS oncogene activation, and suppression of TP 53 (Fearon and Vogelstein, 1990). The CIMP pathway is characterized by promoter hypermethylation of various tumor suppressor genes, most importantly MGMT and MLH1. This hypermethylation is associated with BRAF mutations and microsatellite instability (Weisenberger et al., 2006). The MSI involves the mismatch repair genes mutations which may result from either increased number of short repeated sequences in these genes or its hypermethylation (Sameer et al., 2014). The above mechanisms may result in oncogenesis in colorectal epithelium either separately or they may converge to result in tumour formation (Tariq and Ghias, 2016). The findings above showing different mechanisms of expression of claudin-1 in colorectal cancer may also provide an explanation for those results (Weber et al., 2008; Mees et al., 2009; Singh et al., 2011; Bhat et al., 2012; Kinugasa et al., 2012; Singh et al., 2012).

The value of a modifiable biomarker in a common tumour such as colorectal cancer is promising. Much work remains to be done to answer important questions regarding the utility of such a biomarker in cancer treatment. It is clear that there is a growing consensus with regards to the potential value of claudin-1 as a biomarker of prognostic and therapeutic aspects. Recently, claudin-1 was used to identify endoscopically pre-malignant colonic adenomas using near infrared labelled peptide (Rabinsky et al., 2015). And very recently a traditional Chinese medicine (Antrodia camphorta- AC) was shown to inhibit the epithelial-mesenchymal transition (EMT) phenomenon in-vitro in human colorectal cancer cells through the modulation of claudin-1 and the Wnt/β-catenin signalling pathways. (Hseu et al., 2017).

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