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THE ROLE OF JUNCTIONAL ADHESION MOLECULES IN THE PATHOGENESIS AND PROGRESSION OF COLORECTAL CANCER

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ABSTRACT

Colorectal cancer (CRC) remains a leading cause of cancer mortality globally and is increasing in incidence in the Westernizing world. Junctional adhesion molecule (JAM) family members, JAM-A, JAM-B, JAM-C and Junctional Adhesion Molecule-like protein (JAML), have been implicated in the maintenance of epithelium integrity as well as in the regulation of cellular adhesion and modulation of immune response. Besides their role as molecular junctions, the JAM family of cell adhesion proteins participates in tumor promotion via pro-proliferative signaling acting on the tumor-promoting PI3K/AKT/mTOR axis and enhances both migratory properties, angiogenesis, and immune suppression. In CRC, their expression profile is profoundly altered, with JAM-A and JAM-B typically acting as tumor suppressors, while conversely, JAML acts as a promoter. The expressions of these lncRNAs are aberrant and correlate with tumor stage, metastasis, immune cell infiltration, and patient survival. Some JAM members are downregulated because of promoter hypermethylation, while others become more aggressive in tumours due to overexpression. These data suggest that JAMs would be applicable for biomarkers of diagnosis and prognosis, as well as a molecular target for therapy. Nevertheless, their dual role, being context-dependent, poses challenges in clinical usage. Future studies will explore the utility of molecular profiling and functional analysis of JAM in personalized medicine to improve epithelial barrier function and immunity, thereby providing a potential target for adjunctive immunotherapy.

KEYWORDS: Colorectal cancer, Junctional adhesion molecules (JAMs), PI3K/AKT/mTOR signaling, Biomarkers/therapy.

INTRODUCTION

Colon cancer is the second leading cause of cancer-related deaths globally, with over 1.9 million new cases and 930,000 deaths expected in 2020. The annual incidence of colorectal cancer is projected to increase to 3.2 million new cases and 1.6 million deaths by 2040.[1] The adoption of Western lifestyles in countries with medium to high Human Development Index (HDI) results in higher CRC incidence and mortality rates. Developed nations face the greatest risk of colon cancer, influenced by factors such as obesity, sedentary habits, red meat intake, alcohol, and tobacco use. The development of cancer is influenced by various factors, including life expectancy, education, income, and government health spending.[2,3,4] High-income countries have experienced a decline in colorectal cancer rates due to effective screening programs. Early-stage cancers tend to have higher survival rates than advanced tumors, making timely diagnosis, treatment, and regular follow-up essential for improving survival outcomes and quality of life.[5]

CRC hallmarks include maintaining proliferative signals, avoiding growth suppressors, resisting cell death, enabling replicative immortality, and triggering invasion and metastasis. These characteristics are not distinct, but rather interrelated, with changes in one area frequently effecting others.[6] Cell adhesion molecules (CAMs) such as integrins, cadherins, and CD44 play important roles in cell-cell and cell-matrix interactions, influencing cell proliferation, migration, and survival. Abnormal adhesion properties can speed up cancer progression by promoting cell survival, proliferation, and invasion.[7,8]

The junctional adhesion molecule (JAM) family is a member of the immunoglobulin superfamily, implicated in the formation of tight junctions (TJs) in endothelial and epithelial cells. They contain two V-C2-type Ig-like domains.[9,10] JAM-A, JAM-B, JAM-C, and JAM-L represent the four major members of the JAM protein family.[11] Junctional adhesion molecule-B (JAMB)/JAM-2 is a junctional protein expressed exclusively at intercellular contacts on the cell surface, where it localizes at homotypic junctions. It is predominantly expressed in the heart, endothelium, placental trophoblasts, high endothelial venules, and arteriole endothelial cells.[12,13] JAM-2 plays multiple functions, including the regulation of endothelium and epithelial paracellular permeability, leukocyte trafficking during inflammation, angiogenesis, cell growth, and migration.[14] JAM-2 has become an important topic for future study due to its significance in the integrity of cell junctions. JAM-2 has been shown to interact with JAM-3 in leukocytes involved in trafficking.[15,16,17] JAM-2 has been found to influence melanoma invasion and metastasis through the expression of JAM-3.[18] JAM-2 also promotes JAM-3-dependent gastric adenocarcinoma tumor metastasis.[19] JAM-2 also intervenes in the angiogenic VEGF/VEGFR2 signaling pathway.[20] A recent study revealed that JAM-2 regulates tumor development and angiogenesis.[21] An intriguing observation is that JAM-2 expression is reduced in colorectal cancer due to hypermethylation of its promoter.[22,23,24]

Recent research suggests that JAMs are more than just structural components of tight junctions; they also actively engage in tumorigenic processes such as cell proliferation, epithelial-mesenchymal transition (EMT), migration, immunological modulation, and angiogenesis. In colorectal cancer, abnormal expression and functional dysregulation of JAM family members have been found, leading to epithelial disruption and activation of oncogenic signaling pathways, particularly the PI3K/AKT/mTOR axis. JAMs also alter the tumor microenvironment, which aids in tumor immune evasion and spreading behavior.[25,26]

Although they are gaining in importance, we don’t know nearly as much about how JAMs work in CRC as we do with other adhesion molecules such as cadherins and integrins. The present study aims to provide a thorough summary of the

structural and functional characteristics, the expression profiles, the signaling pathways of JAMs during CRC's development, as well as their diagnostic and therapeutic potentials.

Structure of JAMs

JAMs are classified into four types: JAM1, JAM2, JAM3, and JAM4, sometimes known as JAM-A, JAM-B, and JAM-C.[27,28] They form tight bonds with numerous other adhesion proteins, including JAML, CAR, CLMP, and ESAM.[29] Their distribution in endothelium and epithelial junctions has been determined via research, revealing that they are important regulators of immune responses and vascular homeostasis. Notably, JAMs occur as transmembrane molecules with a single span across the membrane, primarily seen at tight junctions. When activated in conditions such as platelet aggregation, JAMs can be discharged into soluble forms that maintain proinflammatory properties.[30] Similar to other members of the immunoglobulin superfamily, JAMs are structurally tiny proteins with a single-span transmembrane architecture, weighing between 30 and 50 kDa.[31] Their adhesive functions and junctional integrity depend on the intricate interactions, including dimerization and the development of stable homophilic and heterophilic connections that have been disclosed by their crystal structures.[32] JAM's distinct tertiary structures, despite their identical secondary structures, encourage specialized interactions between various JAM types, allowing for improved functioning in cell adhesion and responsiveness to inflammatory stimuli.

JAM-A is recognized as a receptor that activates human platelets and is located in the tight junctions (TJs) of epithelial and endothelial cells, leukocytes, and platelets. This process enhances epithelial barrier function and affects platelet aggregation, inflammation, immune homeostasis, and angiogenesis.[33,34] Likewise, JAM-C, which is found at TJs, shapes epithelial cell motility, polarity, angiogenesis, and vascular permeability. JAM proteins function via three mechanisms: direct cell-cell interaction, surface receptor stability, and interactions with nearby cell receptors. They also control intracellular signaling through PDZ domain-containing proteins.[35,36]

The early phases of metastasis in cancer heavily depend on cell-cell adhesion and migration, and tight junction (TJ) proteins play a crucial role in tumor cell adhesion, polarity, invasion, and migration. According to studies, a decrease in TJ-based adhesion and epithelial barrier function increases cell permeability, which in turn promotes tumor invasion and metastasis. Despite the assumption that TJ proteins operate as tumor suppressors, new research suggests they may drive tumor growth in a context-dependent manner.[37,37,39] For example, JAM-A has been found to promote tumorigenesis and metastasis via adhesion-independent intracellular signaling, despite being related to tumor suppression in some cases. The expression levels of JAM-A differ among cancers, altering patient outcomes.[40,41] Similarly, while JAM-C, another member of the JAM family, is overlooked, it appears to have pro-tumorigenic roles in metastasis, where it is essential for tumor cell adhesion to endothelial cells and intravasation into blood vessels. Further research has linked JAM-C to metastasis in various cancers, including non-small cell lung cancer and melanoma.[42,43]

Expression patterns of JAMs in CRC

The growth of colorectal cancer (CRC) is associated with dysregulation of members of the Junctional Adhesion Molecule (JAM) family, which exhibit distinct expression patterns in colorectal tissues. Normally found at epithelial tight junctions, JAM-A preserves barrier integrity; however, it is frequently diminished or mislocalized in CRC. While normal tissues retain significant expression, this abnormality is seen in more than 50% of primary CRC patients. A higher tumor stage and a worse survival rate are associated with less JAM-A.[44,45] Because of promoter hypermethylation, JAM-B is similarly downregulated in CRC; reviving its expression inhibits the activity of CRC cells.

JAM members play an intricate, context-dependent function in the pathophysiology of colorectal cancer (CRC), as evidenced by the overexpression of JAML in CRC, which promotes cell proliferation through the PI3K/AKT/mTOR pathway.[46,47]

Functional Role of JAMs in CRC

JAM-A was discovered to contribute to the beginning of colorectal tumors and cell proliferation by maintaining epithelial cell polarity and regulating intracellular signaling pathways. The absence of JAM-A led to enhanced crypt fission and proliferation in mouse intestinal tissues, indicating a tumor-suppressive function in the early stages of colorectal cancer formation. JAM-A deletion increases Akt and Erk1/2 phosphorylation, which helps cellular proliferation and disrupts normal epithelial architecture.[48]

Kok-Sin et al studied 150 colorectal tissues using the methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA), and they reported JAM-B was expressed at extremely low levels in colorectal cancer due to JAM-B genes being hypermethylated on promoters in CpG islands.[49] Another recent study addressed gene expression changes associated with cell-cell adhesion in 26 colorectal cancer samples, 42 adenoma samples, and 24 normal mucosa samples. The mRNA levels of the JAM-B genes, which encode adhesion junction proteins, differed among tissue types, with lower expression of JAM-B in adenocarcinoma and adenoma than in healthy colonic mucosa. Furthermore, adenomas had the lowest JAM-B expression levels.[50,51]

JAML is overexpressed in CRC and stimulates tumor proliferation and migration by activating the PI3K/AKT/mTOR axis, as seen by elevated phosphorylation of PI3K, AKT (Ser473), and mTOR (Ser2448) in CRC cell lines. Inhibiting mTOR partly inhibited JAML-mediated proliferation and migration.[25] JAM-A expression on immunological and endothelial cells may affect leukocyte trafficking and cytokine networks in the tumor microenvironment. In mouse models, JAM-A deletion increased dendritic cell and T-cell infiltration and decreased cancer development.[52] Based on these observations, it appears that members of the JAM family affect inflammation, immunological infiltration, and angiogenesis in the CRC tumor microenvironment.

Several recent studies investigated the role of junctional adhesion molecules, such as protein (JAML), in colorectal cancer (CRC). Feng et al. (2024) discovered that more than half of the CRC patient samples overexpressed JAML. In general, higher levels were linked to advanced tumor stages and lower overall survival rates. Reduced tumor-infiltrating lymphocytes (TILs) were also associated with increased JAML expression, suggesting a role in immune evasion. JAML activated the PI3K/AKT/mTOR pathway, increasing cancer cell motility, invasion, and proliferation. Reducing JAM expression in CRC cell lines reversed these effects, indicating that it can be used as both a symptomatic marker and a therapeutic target, particularly in patients who avoid immunotherapy.[53]

Clinical Implications of JAMs in Colorectal Cancer

Junctional adhesion molecule (JAM) expression variations are associated with the onset, metastasis, and prognosis of colorectal cancer (CRC). Lampis et al. discovered that suppressing JAM-A in CRRC, primarily through microRNA-21 overexpression, increased the activation of oncogenic ER-K, ATC, and ROSK signaling pathways. Clinical testing revealed loss of JAM-A in more than half of the investigated CRC samples; it was associated with advanced cancer and decreased patient lifespan, indicating its potential as a predictive biomarker.[54]

JAM-like protein (JAML) has been identified as a pro-tumorigenic member of the JAM family in CRC. Feng et al. According to the findings, JAML was overexpressed in nearly 50% of CRC tumor samples, and high expression was associated with advanced TNM stage and poor overall survival. Mechanical investigations have demonstrated that JAML enhances tumor growth, migration, and invasion by activating the PI3K / AKT / mTOR signaling pathway. Additionally, JAML overexpression was linked to fewer tumor-infiltrating lymphocytes (TILs) and lower levels of T-cell-recruiting chemokines such as CCL20 and CXCL 9/10/11, indicating an additional involvement in immune evasion. Silencing JAML expression, on the other hand, reversed these effects, indicating that it has the potential to be both a prognostic marker and a therapeutic target in CRC.[52]

The CRC also includes additional JAM family members, most notably JAM-B (JAM-2). Wang et al. discovered that promoter hypermethylation typically lowered JAM-b expression in CRC tissues. Functional experiments revealed that JAM-B loss enhanced cancer cell proliferation and migration, suggesting a tumor-suppressive effect in this environment.[55]

According to these findings, JAMs have context-dependent roles within CRC; certain members, such as JAM-A and JAM-B, exhibit tumor-suppressive qualities, whilst others, such as JAML, operate as oncogenic drivers. Their high correlation with metastasis, tumor stage, immunological regulation, and patient survival lends credence to JAMs' potential as a diagnostic/symptomatic biomarker and therapeutic target in colorectal cancer.

CONCLUSION

The junctional adhesion molecule (JAM) family has several roles in colorectal cancer (CRC), including acting as active tumor growth modulators and providing structural features of tight junctions. Their activities in the tumor microenvironment include maintaining epithelial integrity, facilitating cell migration, promoting proliferation, supporting angiogenesis, and mediating immunological interactions. There is a clear functional duality: JAM-A and JAM-B uphold barrier function and inhibit malignant development, but JAML has been linked to PI3K/AKT/mTOR signaling activation and suppression of immune surveillance. Clinically, abnormal JAM expression is associated with advanced disease, metastatic spread, and poor survival, making them valuable biomarkers and therapeutic targets. However, many of their activities pose challenges: protective and oncogenic JAM functions need to be distinguished for effective treatment. It is exciting to consider JAM-targeted medicines integrated into the immunotherapy framework, especially in precision oncology, where immune regulation is crucial.[56,57]

In the future, large-scale multi-centre studies are required to evaluate the prognostic and predictive significance of certain JAM members, such as early-onset CRCs, where their involvement is unknown. Analysing databases like The Cancer Gene Atlas (TCGA) might help explain the patterns of JAM expression in various tumor types.[58] At the same time, functional investigations on adhesion-related genes in CRCs have revealed considerable alterations in cell-cell adhesion pathways[59], demonstrating the broad impact of junctional proteins on tumor biology. The discovery of JAM-specific therapies might result in novel targeted methods to inhibit tumor growth and restore effective anti-tumor immunity.

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