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Junctional adhesion molecules in cancer: a paradigm for the diverse functions of cell-cell interactions in tumor progression

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Abstract

Tight junction (TJ) proteins are essential for mediating interactions between adjacent cells and coordinating cellular and organ responses. Initial investigations into TJ proteins and junctional adhesion molecules (JAM) in cancer suggested a tumor suppressive role where decreased expression led to increased metastasis. However, recent studies of the JAM family members JAM-A and JAM-C have expanded the roles of these proteins to include pro-tumorigenic functions, including inhibition of apoptosis and promotion of proliferation, cancer stem cell biology, and epithelial-to-mesenchymal transition. JAM function by interacting with other proteins through three distinct molecular mechanisms: direct cell-cell interaction on adjacent cells, stabilization of adjacent cell surface receptors on the same cell, and interactions between JAM and cell surface receptors expressed on adjacent cells. Collectively, these diverse interactions contribute to both the pro- and anti-tumorigenic functions of JAM. In this review, we discuss these context-dependent functions of JAM in a variety of cancers and highlight key areas that remain poorly understood, including their potentially diverse intracellular signaling networks, their roles in the tumor microenvironment, and the consequences of post-translational modifications on their function.

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These studies have implications in furthering our understanding of JAM in cancer and provide a paradigm for exploring additional roles of TJ proteins.

Keywords

junctional adhesion molecules; cell adhesion; cell junctions; review

Introduction

Junctional adhesion molecule A (JAM-A), also known as JAM-1 or F11R, is the founding member of the JAM sub-family, one branch of the larger immunoglobulin superfamily (IgSF) of cell surface proteins. JAM-A, JAM-B, and JAM-C, the focus of this review, are classical JAM molecules that display up to 35% amino acid sequence homology and contain a short cytoplasmic tail (40–50 residues) with a class II PSD-95/Discs-large/ZO-1 (PDZ) domain-binding motif at the C-terminus. There are also additional JAM-related proteins, including JAM-4, JAM-L, CAR, CLMP and ESAM, which have a long cytoplasmic tail (98–120 residues) with a class I PDZ domain-binding motif (1). JAM-A was originally identified as the receptor of a monoclonal antibody that activates human platelets (2) and is expressed in the tight junctions (TJs) of both epithelial and endothelial cells, as well as some leukocyte populations and platelets (3,4). Like other TJ proteins, JAM-A mediates epithelial barrier function but also has roles in platelet aggregation and hemostasis, inflammation and immune homeostasis, and angiogenesis (5). Similarly, JAM-C is found at TJs, where it regulates epithelial cell migration, cell polarity, angiogenesis and vascular permeability (6). JAMs mediate these functions through three distinct molecular mechanisms, including (a) direct cell-cell interaction between adjacent cells, (b) stabilization of adjacent cell surface receptors (such as integrins) on the same cell, and (c) interactions with cell surface receptors expressed on adjacent cells (7). These mechanisms control intracellular signaling potentially through interactions with a few well-characterized PDZ domain-containing proteins, which are mediated through the C-terminal PDZ domain-binding motif (see JAM-A Structure and Function section below) (5).

In cancer, cell-cell adhesion and migration are essential processes that occur during the early stages of metastasis. As such, TJ proteins have well-established roles in tumor cell adhesion, polarity, invasion and migration. Prior landmark studies have demonstrated that the lack or loss of TJ-based cell adhesion and epithelial barrier function increases cell permeability, leading to increased tumor cell invasion, dissemination and metastasis (8,9). However, an increasing number of studies suggest that TJ proteins may not function as tumor suppressors but rather accelerate tumor progression, suggesting that TJ proteins function in a context-dependent manner in cancer (10). This context-dependent function has also been reported for JAM-A, as multiple studies have demonstrated that increased JAM-A expression drives tumorigenesis and promotes metastasis by activating adhesion-independent intracellular signaling pathways (11–13). Similarly, there are also reports that support a tumor-suppressive role for JAM-A (14,15). These functional differences are also reflected in an increase or decrease in JAM-A levels across a variety of cancers that either positively or negatively correlates with patient prognosis (16–19). For this reason, there is no clear

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consensus for the function of JAM-A in cancer, likely reflecting the complexity of the three main mechanisms of interaction of JAM-A and resulting diversity in downstream signaling. The expression of JAM-B is primarily limited to endothelial cells and hence is not discussed here.

While less studied, there is evidence for pro-tumorigenic functions of JAM-C, another JAM family member expressed on epithelial cells, primarily in metastasis. Studies in the early 2000s identified JAM-C as necessary for both adhesion of tumor cells to endothelial cells (20) and for tumor cell intravasation into blood vessels (21), and the RVE sequence in the amino terminal Ig domain was responsible for this binding (see JAM-A Structure and Function section below). A number of follow-up studies across a wide array of cancers have likewise implicated JAM-C in metastasis, including in non-small cell lung cancer (NSCLC) (22), melanoma (23,24), fibrosarcoma (25), ovarian cancer (26), gliomas (27), renal cell carcinoma (28) and multiple liquid tumors (29–31). Here, we discuss the underlying mechanisms through which JAMs function, using JAM-A as an illustrative example, to either suppress or drive tumor progression and examine how JAMs can serve as a paradigm to reveal additional roles for other TJ proteins in complex cancer phenotypes.

JAM-A structure and function

Given the diversity of cell types and tissues in which JAM-A is expressed, this protein is likely involved in the regulation of numerous physiological processes, ranging from intercellular TJ assembly critical for maintaining junctional integrity and permeability to cellular polarity, leukocyte transendothelial migration, platelet aggregation, and angiogenesis (32–38). All JAM family members are type I transmembrane glycoproteins and share a similar structure, which includes two extracellular immunoglobulin-like domains at the N-terminus, a transmembrane region, and a cytoplasmic tail of variable length within the C-terminus of the protein. The extracellular segment of JAM-A is composed of a membrane-distal V-type Ig domain that contains cis-dimerization and trans-homophilic interaction motifs, which are thought to mediate adhesive interactions, and a membrane-proximal C2-type domain (5). The cytoplasmic tail of JAM-A is short, consisting of only 40 amino acid residues with no known catalytic activity. However, the cytoplasmic tail contains a PDZ domain-binding motif, which can directly interact with scaffolding cytoplasmic proteins such as ZO-1, ZO-2, Patj, Afadin, ASIP/Par3, CASK, MUPP1, MAGI-1, and PDZ-GEF2. These binding partners are reviewed in greater detail elsewhere (Ebnet et al 2017)(7,39,40) and likely represent only a subset of the total binding proteins that mediate JAM signaling.

Additionally, the cytoplasmic tail of JAM-A has 13 amino acids that could potentially be phosphorylated, two of which have been shown to be functionally important (Y280 and S284). In epithelial cells, residue Y280 of JAM-A is phosphorylated at low levels at baseline; however, after treatment with TNF-α, IFNγ, IL-22 or IL-17A, phosphorylation increases as a result of Yes-1 kinase and PTPN13 phosphatase regulation (41). Additionally, when endothelial cells are treated with fibroblast growth factor (FGF), the presence of a single Y280F mutant protein prevents FGF-mediated p44/42 MAPK activation (42,43). In platelets, Ser284 is phosphorylated by PKCα in response to thrombin or collagen (44), whereas in epithelial cells, Ser284 is phosphorylated by aPKCζ and is thought to be

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important for TJ formation (45). Finally, the extracellular domain contains a single known site for N-glycosylation (N185), which stabilizes JAM-A, enabling more efficient trans-homophilic binding (46). While these post-translational modifications are known to regulate JAM-A function, little is known about these modifications in the context of cancer.

Given the numerous functions of JAM-A in normal physiology, it is not surprising that JAM-A exhibits a multitude of functions in tumor growth and metastasis in different tumor types. This is highlighted by the diverse expression profiles of JAM-A across tumor types, where both decreased and increased expression of JAM-A are associated with tumor progression and poor prognosis (Table 1). In addition to maintaining epithelial cell barrier integrity, JAM-A also regulates proliferation and differentiation. Dysregulation of JAM-A intercellular adhesion, polarity, or signaling promotes tumorigenesis through increased proliferation and migration. Finally, JAM-A has been shown to be critical for cancer stem cell (CSC) maintenance (11,47) and induces epithelial-to-mesenchymal transition (EMT) in some cancers (12).

Regulation of JAM-A expression

JAM-A expression can be regulated at the epigenetic, mRNA or protein level. Histone acetylation regulates JAM-A expression, as deacetylase inhibitors have been shown to lead to increased JAM-A production in multiple myeloma (48). Regulation of JAM-A expression by microRNAs is also well established (49–51). In this regard, breast cancer cell motility and invasiveness are controlled by microRNAs (e.g., miR-145 and miR-495)(51). miR-145 has also been shown to be reduced in glioblastoma CSCs, where its overexpression leads to decreased JAM-A expression and loss of CSC maintenance (49). In a model of migration and invasion of human prostate epithelial cellsty the SNARE protein Ykt6 was also shown to negatively regulate JAM-A expression through miR-145 (52). In addition to miR-145, miR-495 was shown to induce breast cancer cell migration by targeting JAM-A (51). To date, few efficacious JAM-A targeted treatments exist; however, a more in-depth understanding of JAM-A regulation may yield other targetable proteins that regulate JAM-A expression or function.

Cell proliferation and apoptosis

Most studies reveal that elevated JAM-A expression in cancer cells increases their proliferation and inhibits their death by apoptosis (13,16,53–56). Outside of genetic gain- and loss-of-function studies, a JAM-A antibody (6F4) has been developed that accelerates the internalization and downregulation of JAM-A and attenuates tumor proliferation in breast cancer cells (53). JAM-A expression using a different JAM-A neutralizing antibody (BV11) induces cell apoptosis and reduces cell growth in mammary tumor cells (13). Of note, these antibodies are thought to target JAM-A through different mechanisms from the well-described J10.4 antibody, which prevents JAM-A dimerization (57). JAM-A knockdown similarly decreases the proliferation of gastric cancer cells and the expression of the anti-apoptotic protein Bcl-xL (54). In addition, JAM-A knockdown with siRNA inhibited tumor cell proliferation and induced cell cycle arrest at the G1/S boundary in NSCLC (16). In another lung cancer study, treatment of a lung adenocarcinoma cell line (LHK2) with an

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anti-JAM-A antibody significantly reduced cell proliferation and promoted apoptosis, and JAM-A knockout tumors were smaller *in vivo* (58).

JAM-A interactions with other cell surface receptors are also important for the promotion of proliferation and the inhibition of apoptosis. Elevated JAM-A levels are associated with increased HER2 expression, through regulation of HER2 protein degradation. JAM-A also assists in HER2 signaling in HER2-positive breast cancer cells via AKT, suggesting that JAM-A may be a potential therapeutic target in the setting of HER2-positive breast cancer (55)(Fig 1). Follow-up studies found that JAM-A was highly expressed in HER2 therapeutically resistant tumors due to cleavage of JAM-A by ADAM-10 and enhanced breast cancer invasion and proliferation. This finding suggests that JAM-A overexpression and cleavage drive tumorigenic behavior and indicate that JAM-A may act as a biomarker for resistance to HER2-targeted therapy (59). More recently, it was observed that downregulation of JAM-A and HER2 by the natural compound tetrocarcin-A caused caspase-dependent apoptosis of primary breast cells and lung CSCs and inhibited the growth of xenografts *in vivo* (56). Similarly, tetrocarcin-A induced apoptosis and reduced cell viability in a triple-negative breast cancer (TNBC) model through downregulation of JAM-A and reduced phosphorylation of ERK (56).

However, there are also reports that JAM-A functions in a tumor suppressive role by increasing apoptosis and suppressing proliferation. A study in colorectal adenocarcinoma revealed that loss of JAM-A expression increased intestinal epithelial cell (IEC) proliferation in SKCO-15 cells through the inhibition of Akt-dependent β-catenin activation (60). These studies indicate that regulation of JAM-A expression in the context of cell proliferation may operate in tissue- and cell-specific contexts. Determining how JAM-A functions in a cell type- or tissue-specific manner is an avenue for future study. One area that warrants further investigation is the role of the local microenvironment. For example, FGF has been shown to rely on JAM-A expression in multiple cell contexts, suggesting that the role of JAM-A in proliferation may depend on whether certain cell types rely on FGF for growth (42,61). A further understanding of the proteins with which JAM-A interacts and how these interactions may alter downstream signaling is essential to improve our understanding of the function of JAM-A in cell proliferation and apoptosis. Finally, the role of JAM-A *in vitro* may depend on the culture conditions. A study of breast cancer cell lines found that cells cultured at a high cell density have lower expression of JAM-A compared to sparse cultures (62).

Metastasis: the integration of cell migration, invasion and metastasis

Metastasis is the primary cause of cancer mortality and remains difficult to treat. The metastatic cascade represents a multi-step process that includes local tumor cell invasion, transendothelial migration of cancer cells into vessels (intravasation), the presence of circulating tumor cells (CTCs) within the bloodstream and their extravasation from the circulation, and colonization in distant organs (63). CTCs are considered to be the precursors of metastasis and play critical roles in tumor metastasis in various cancer types; as such, CTC clusters have high metastatic potential (64,65).

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Based on the function of JAM-A in maintaining TJ integrity and regulating cell-cell adhesion, one study assessing invasive breast cancer found that cell lines with the lowest migratory capacity (T47D and MCF-7 cells) express higher levels of JAM-A relative to more migratory lines (MDA-MB-231 cells). Ectopic expression of JAM-A in these highly metastatic cells attenuated both cell migration and invasion, whereas silencing of JAM-A expression enhanced the invasiveness of the less migratory lines (14). Similarly, transforming growth factor-β1 (TGF-β1) induced invasion of MCF-7 cells through downregulation of JAM-A expression, such that reduced TGF-β receptor expression and canonical Smad signaling increased JAM-A levels and inhibited cell invasion (66).

However, an emerging body of evidence supports a function for JAM-A as a positive regulator of cell migration and invasion, where JAM-A downregulation inhibits the migration and invasiveness of a variety of cancer types. Human nasopharyngeal cancer cells exhibit increased JAM-A levels, which leads to increased EMT via activation of the PI3K/AKT pathway (12). In lung adenocarcinoma, the suppression of JAM-A expression by siRNA transfection inhibited cellular motility and invasiveness, while JAM-A inhibition caused a decrease in colony-forming capability *in vitro* and an inhibition of tumorigenicity *in vivo* (58). Functional inhibition of JAM-A protein activity also inhibited the adhesion and transendothelial migration of breast cancer cells (67).

JAMs interact in cis and trans with a variety of integrins, both α and β, across a variety of physiological contexts (68). The interactions among JAM-A, β1 integrin, and Rap1 were first established in colonic epithelial cells, where they promote cell migration (69). Follow-up studies in breast cancer have shown that JAM-A knockdown reduces breast cancer cell adhesion and migration through activation of Rap1 GTPase and β1 integrin signaling (70). Of interest, these interactions are thought to be dependent on N-glycosylation of the asparagine amino acid at position 185, a posttranslational modification that warrants further investigation in the setting of cancer (46).

The functional roles of JAM-A in tumor invasion and metastasis have not been fully elucidated. These reported differences likely reflect the underlying mechanisms driving each particular tumor cell state. In settings where JAM-A interacts with its neighbors to form strong tight junctions, loss of JAM-A is likely associated with metastasis. In contrast, when JAM-A functions through integrin β1 and Rap1, overexpression of JAM-A likely contributes to metastasis. It is also reasonable to hypothesize that in a different stages of metastasis, JAM-A might have different functions. For example, loss of JAM-A may be essential for local invasion, whereas during extravasation, colonization, and proliferation of metastatic lesions, elevated expression of JAM-A may be necessary for tumor progression. Another possible explanation is that different categories of binding (i.e., homophilic and heterophilic, cis and trans) may facilitate opposite functions. Therefore, a simple assessment of JAM-A expression may not provide a clear enough picture of what happens in an in vivo tumor setting. Additional studies are required to elucidate the molecular mechanisms and functional roles of JAM-A in tumor progression and metastasis. Conceptually, this could also provide new information into the mechanisms through which TJ proteins function during metastasis. For example, coxsackievirus and adenovirus receptor (CAR), another tight junction protein of the Ig superfamily, has been shown to be increased in breast and

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other cancers. While most studies have investigated its role in metastasis (71), CAR may also play a role in the inhibition of apoptosis (72).

The role of JAM-C as a pro-tumorigenic protein

While JAM-A appears to have a variety of functions in cancer cells, our current understanding of JAM-C has focused on metastasis. JAM-C has both extrinsic and intrinsic functions within cancer cells. JAM-C expression on endothelial cells has also been shown to be necessary for tumor development, an example of an extrinsic function. In a model of ovarian cancer, knockout of JAM-C on endothelial cells resulted in reduced pericyte coverage and increased vascular leakage, leading to longer mouse survival (26). In addition to binding to JAM-C on endothelial cells, JAM-C also binds to JAM-B, which can stimulate tumor cell metastasis and invasion (27,73) (Fig 1). In a tumor cell-intrinsic manner, JAM-C is thought to control the activation of SRC family kinases and lead to ERK phosphorylation, which activates the machinery required for migration and invasion (27,29,30). JAM-C dimerization, either as a homodimer or a heterodimer with JAM-B, appears to be essential for cell migration, polarization and adhesion. The amino acids E66 and K68 are critical for JAM-C dimerization, and mutation of these residues diminishes the pro-metastatic function of JAM-C (20,74).

Numerous approaches for disrupting JAM-C have been developed. In one study, soluble JAM-C prevented the development of lung metastases in the B16 melanoma model (75). Additionally, anti-JAM-C polyclonal antibodies were found to reduce the homing of B cells to lymphoid organs in a model of mantle cell lymphoma (30). Finally, in glioblastoma, a tumor type with significant invasion into the neighboring parenchyma, anti-JAM-B/C blocking antibodies decreased tumor growth and invasion (27). These studies highlight the therapeutic potential of disrupting JAM-C interactions to limit metastasis and invasion. While these treatments are unlikely to demonstrate any tumor cell cytotoxicity, they may be utilized to prevent or limit metastasis in various tumors.

JAM-A in the immune tumor microenvironment

Within the immune system, where a unique function of JAM-A was first described and mediated by JAM-A/integrin binding between adjacent cells (68), JAM-A is highly enriched in cells of the myeloid lineage, including monocytes, macrophages, and microglia, the resident immune cell of the brain. Specifically, within the mouse and human nervous systems, JAM-A is highly expressed in microglia/macrophages and endothelial cells. In the setting of HIV infection, migration of $CD14^+$ $CD16^+$ monocytes into the brain can be blocked by JAM-A neutralizing antibodies (76). Loss of JAM-A impairs peritoneal macrophage chemokine-induced neutrophil migration (77). Lastly, JAM-A expression was higher in microglia relative to bone marrow-derived macrophages (78), whereas brain-infiltrating macrophages acquire JAM-A expression in the setting of experimental high-grade glioma and following bone-marrow transplantation. In this respect, JAM-A expression on microglia reduces the aggressiveness of glioblastoma by limiting microglial activation. Interestingly, this observation was only observed in females, suggesting that JAM-A may function in a sex-specific manner (79). To our knowledge, this is one of the few studies

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investigating JAM-A within the TME. However, with the widespread expression of JAM-A in various tumors, stromal cell-expressed JAM-A is likely to play similar roles in other cancers. Precise methodologies such as single-cell sequencing should enable the identification of other cell populations within human tumors that express JAM-A and other JAM family members. Additionally, given their established role in mediating leukocyte trafficking (80), defining how JAM-A/C function to govern leukocyte infiltration into the tumor microenvironment (TME) may have relevance to future immunotherapy approaches. While the majority of JAM-A cancer research has focused on JAM-A expression in malignant cells, these studies highlight the importance of tumor cell-stromal interactions.

JAM-A expression and clinical outcomes in cancer

In breast cancer, JAM-A expression was initially found to be differentially expressed in normal breast epithelium, adjacent primary tumors, malignant tumors, and matched lymph node breast metastases, with a lower level of expression in metastatic lesions (14). However, analysis of several larger patient datasets demonstrated a positive correlation between JAM-A expression and poor patient outcome (13,17,55), such that high levels of JAM-A expression were associated with worse patient survival. Of note, increased JAM-A expression in ductal carcinomas compared to lobular carcinomas has been reported, and this may help to explain some of the contradictory results found in other studies (13).

In other types of cancer, JAM-A dysregulation similarly correlated with tumor progression and prognosis. JAM-A overexpression has been reported to promote tumor progression and is associated with a poor prognosis in lung cancer (16,53,58,81), ovarian cancer (82), glioblastoma (11,83), nasopharyngeal cancer (12,84), and oral squamous cell carcinoma (85). However, low expression of JAM-A in pancreatic cancer was associated with poor patient overall survival (19). Additionally, decreased JAM-A expression was also associated with tumor progression and poor patient survival in gastric cancer (18) and anaplastic thyroid carcinoma, where lower JAM-A expression correlated with extrathyroid infiltration and a larger tumor size (86).

The correlation between the aberrant JAM-A expression in tumor tissues and clinical outcome has been investigated across a diverse range of tumor types. Although numerous studies have looked at the correlation between JAM-A expression and prognosis, clinical data and stratified analysis are very limited, and the clinical significance of JAM-A expression for diagnosis, prognosis, and drug resistance remains an active area of research (Table 1). Further studies are needed to clarify the diverse roles of JAM-A for future diagnostic and therapeutic applications.

Conclusion

The initial assessments of TJs in cancer suggested a tumor suppressive role, with loss/reduction resulting in increased metastasis. However, recent evidence has expanded the possible functions of the JAM family of proteins in cancer, including apoptosis, proliferation, CSC maintenance and EMT. As described herein, both pro-tumorigenic and anti-tumorigenic roles of JAM-A have been reported (Fig. 1). While the majority of recent

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studies support a pro-tumorigenic function, one cannot ignore the numerous studies that provide evidence for a tumor suppressive role. JAM-A may have pro-tumorigenic functions in some cancers (glioblastoma and NSCLC), while in other tumors (pancreatic cancer and gastric cancer), loss of JAM-A expression is associated with tumor progression. JAM-B/C on the other hand appear to play a role in metastasis, and all data to this point support a pro-tumorigenic role. The possibility remains that JAM-B/C have other cell signaling functions that have yet to be elucidated.

While the presence or absence of JAMs within a tumor provides a starting point for our understanding, future studies should prioritize investigating the role of post-translational modifications. JAM-A phosphorylation and N-glycosylation have been studied in other fields and appear to be important for JAM-A function. However, very little is known about the roles these modifications play in cancer. Additionally, JAM proteins could undergo other post-translational alterations. In parallel, the identification of novel binding partners required for intracellular signaling is also essential. The majority of studies identifying JAM-A binding targets were performed using epithelial cells, where JAM-A canonically functions as a tight junction protein. However, the identification of additional JAM-A interacting proteins is essential to elucidate its mechanism(s) of action in other cell types in neoplasia that may utilize a different repertoire of binding partners and downstream signaling networks. Finally, the role of these proteins in non-neoplastic cells within the tumor microenvironment should be further investigated. In this respect, JAM function in endothelial cells, pericytes and monocytes warrants more in-depth study.

Lastly, our expanded understanding of JAMs in cancer has the potential to inform new roles for other TJ proteins in the process of tumorigenesis and progression. As JAM-A highlights, these proteins have a wide range of functions outside of mere cell adhesion and could represent future potential targets for cancer prognosis and treatment.

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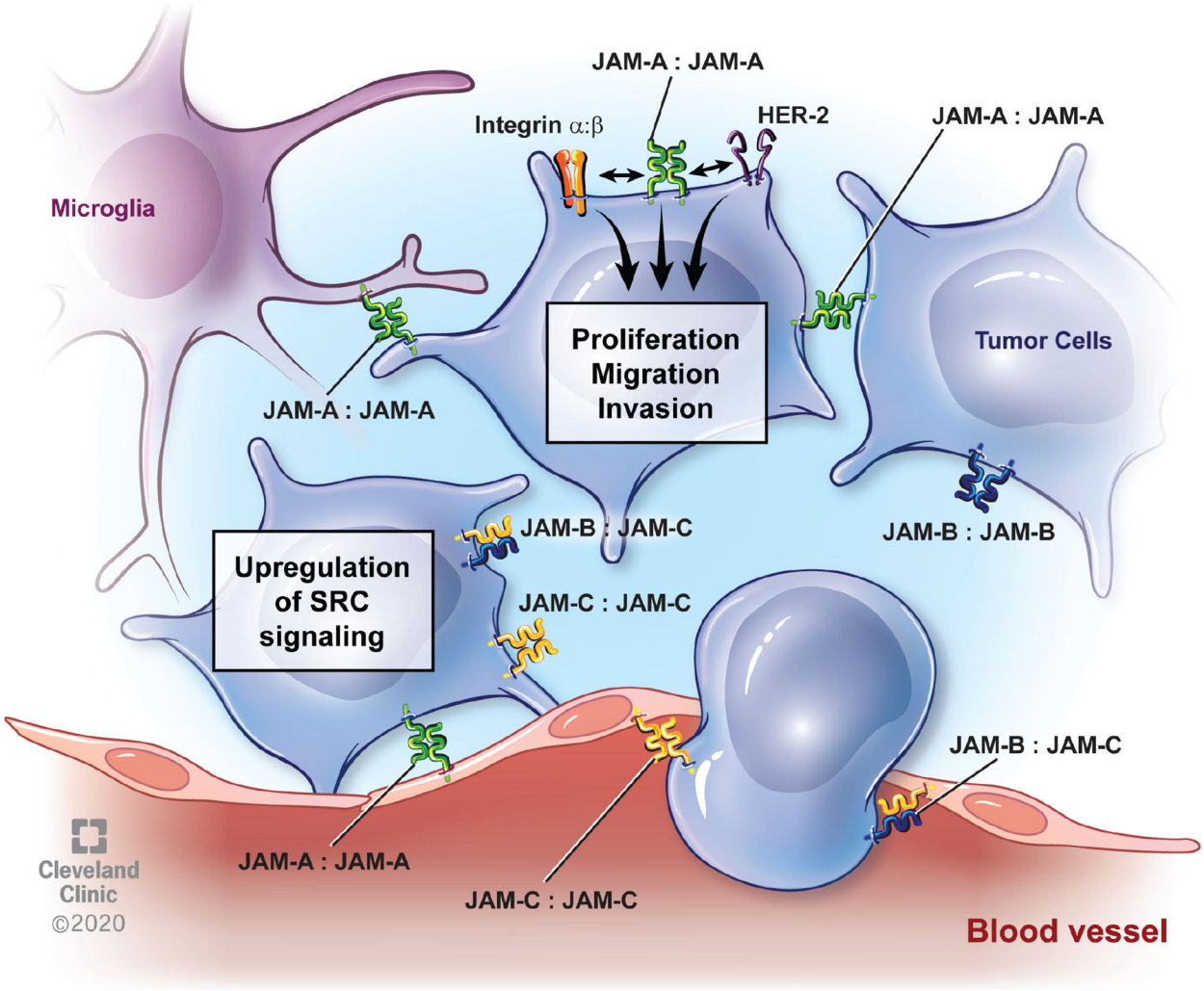

Figure 1. Summary of JAM interactions within the tumor microenvironment.

JAM-A expressed on tumor cells interacts with numerous other proteins to stimulate tumor cell proliferation, migration, invasion and metastasis and to inhibit apoptosis. The role of JAM-A in the tumor microenvironment, particularly in microglia and macrophages, is currently being investigated. JAM-C is essential for metastasis, a process mediated by JAM-B on endothelial cells through increased tumor cell extravasation.

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Table 1.

JAM-A expression in different tumors and its association with clinical outcome

Type of cancer	JAM-A level compared to normal tissue	JAM-A correlation with poor prognosis	Refs
Breast	Mixed	Positive	(13,14,17,55)
Lung	Increased	Positive	(16,53,58,81)
Gastric	Decreased	Negative	(18)
Pancreatic	Decreased	Negative	(19)
Glioblastoma	Increased	Positive	(11,49,83)
Nasopharyngeal	Increased	Positive	(12,84)
Oral squamous cell carcinoma	Increased	Positive	(85)
Ovarian	Increased	None	(82)
Anaplastic Thyroid	Decreased	Unknown	(86)

Increased/decreased denotes JAM-A expression in tumor cells compared to normal tissue. Positive/negative denotes the correlation between JAM-A and poor prognosis in each tumor.