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Junctional Adhesion Molecules (JAMs) - New Players in Breast Cancer?

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1. Introduction

1.1 Global incidence of breast cancer

Worldwide, breast cancer remains a leading cause of death amongst women. Annually, it is estimated that breast cancer is diagnosed in over a million women (Kasler *et al.*, 2009) with over 450,000 deaths worldwide (Tirona *et al.*, 2010). The incidence of the disease is highest in economically-developed countries, with lower rates in developing countries. Despite continual advances in breast cancer care which have led to reduced mortality, however, the incidence of the disease is still rising. The decrease in breast cancer-specific mortality has been attributed to improvements in screening techniques which permit earlier detection, surgical and radiotherapy interventions, better understanding of disease pathogenesis and utilization of traditional chemotherapies in a more efficacious manner. Consequently, early stage breast cancer is now a curable disease while advanced breast cancer remains a significant clinical problem.

Breast cancer is a heterogeneous disease encompassing many subtypes, which differ both in terms of their molecular backgrounds and clinical prognosis. These breast cancer subtypes range from pre-invasive early stage disease to advanced invasive disease. The simplest classifications of disease subdivide breast cancer into pre-invasive and invasive forms; with the pre-invasive forms being ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS). Carcinoma *in situ* is proliferation of cancer cells within the epithelial tissue without invasion of the surrounding stromal tissue (Bland & Copeland, 1998). DCIS arises in the terminal ductal lobular units (TDLU) and in extra-lobular ducts while LCIS occurs in the breast lobules, and is recognisable histopathologically by the presence of populations of aberrant cells with small nuclei (Hanby & Hughes, 2008). Invasive breast cancers are sub-classified into invasive ductal breast cancer, invasive lobular breast cancer, inflammatory breast cancer and Paget's disease. Invasive ductal carcinoma (IDC) is the most common form of invasive breast cancer, accounting for around 85% of all cases.

DCIS is frequently considered as an obligate precursor to IDC, progressing from lower to higher grades and then onto invasive cancer with progressive accumulation of genomic changes (Farabegoli *et al.*, 2002). However it has alternately been suggested that there exist genetically-distinct subgroups of DCIS, only some of which have the potential to progress to invasion (Shackney & Silverman, 2003). Long-term natural history studies of DCIS have provided supportive evidence for both possibilities (Page *et al.*, 1995; Collins *et al.*, 2005; Sanders *et al.*, 2005). Despite such controversies, the large extent to which the genome is

altered in DCIS strongly suggests that genomic instability precedes phenotypic evidence of invasion (Hwang *et al.*, 2004). This serves to underline the fact that malignant transformation in a heterogeneous disease like breast cancer is a dynamic process evolving through multiple multi-step pathway models.

Many factors are thought to be responsible for the development of breast cancer. Genetic factors play a vital role in the predisposition to breast cancer, with mutations of *BRCA1* and *BRCA2* genes accounting for 5–10% of breast cancer cases and being responsible for 80% of inherited breast cancers (Nathanson *et al.*, 2001). On a more complex level, much insight has been gained from the genetic profiling of thousands of tumours to generate gene signatures of prognostic value (Sorlie *et al.*, 2001; van 't Veer *et al.*, 2002; van de Vijver *et al.*, 2002), which have spurred the development of commercially-available diagnostic tests. The importance of reproductive factors in the aetiology of breast cancer is also well recognised with early onset of menarche, nulliparity, late menopause, endogenous and exogenous hormones representing the main risk factors (Reeves *et al.*, 2000; Key *et al.*, 2001; Howell & Evans, 2011). Several other studies have reported an increased risk of breast cancer with lack of physical activity (especially in pre menopausal women), as well as increasing age and obesity (Clarke *et al.*, 2006; Walker & Martin, 2007; Harrison *et al.*, 2009; Rod *et al.*, 2009; Awatef *et al.*, 2011). These risk factors accentuate the abnormal growth control of cells by increasing the circulating levels of oestrogen thereby promoting tumourigenesis within the breast microenvironment. A proper understanding of the breast cancer microenvironment is essential for understanding breast cancer, and will be explored in detail in the next sections.

1.2 Breast structure and breast cancer microenvironment

The breasts are modified sweat glands with a specialized function to produce milk. In the adult, the mature breast extends from the second ribs to the seventh rib and from the lateral border of the sternum to the midaxillary line and projects into the axilla at the axillary tail of Spence (Monkhouse, 2007). The breast is located within the superficial fascia of the anterior thoracic wall and is made up of 15-20 lobes of glandular tissue (Bland & Copeland, 1998). Fibrous connective tissue forms the framework that supports the lobes and adipose tissue which fills the space between the lobes. Each lobe of the mammary gland terminates in a lactiferous duct which opens onto the nipple and is lined with breast epithelial tissue. These ducts have a sinus at the base beneath the areola called the lactiferous sinus (Figure 1).

Breast cancers are characterised by abnormal proliferation of breast epithelial cells and mostly originate in milk ducts (Sainsbury *et al.*, 2000). Normal milk ducts consist of an outer myoepithelial cell layer and an inner luminal epithelial layer. Myoepithelial cells, which are of ectodermal origin, lie between the surface epithelial cells and the basal lamina. Both the epithelial and myoepithelial cells of the breast duct lie on a basement membrane composed of extracellular matrix factors secreted by those cells (Figure 2). The basement membrane is important for defining the barriers of the normal duct, and thus alterations in the basement membrane have been implicated in abnormal cell differentiation and the formation of metastases (Kleinman *et al.*, 2001).

Proliferation of cells within the breast ducts is controlled by growth-promoting proto-oncogenes and growth-inhibiting tumour suppressor genes. In most cases, normal cells divide as many times as needed and then stop. Carcinogenic mutations in either (or both)

oncogenes and tumour suppressor genes (along with subsequent interactions between defective genes and the breast microenvironment) alter not just cell proliferation, but also differentiation, survival and genome stability (Hahn & Weinberg, 2002) of breast cells, leading to abnormal cell growth and potentially cancer.

Much evidence supports the contention that the pathogenesis of breast cancer is influenced by complex interactions between ductal epithelial cells and the cells that compose the tumour microenvironment (Weaver *et al.*, 1996; Polyak & Hu, 2005; Hu *et al.*, 2008). The next section will focus on the cells of the microenvironment with respect to normal breast tissue structure and also their possible involvement in breast tumourigenesis.
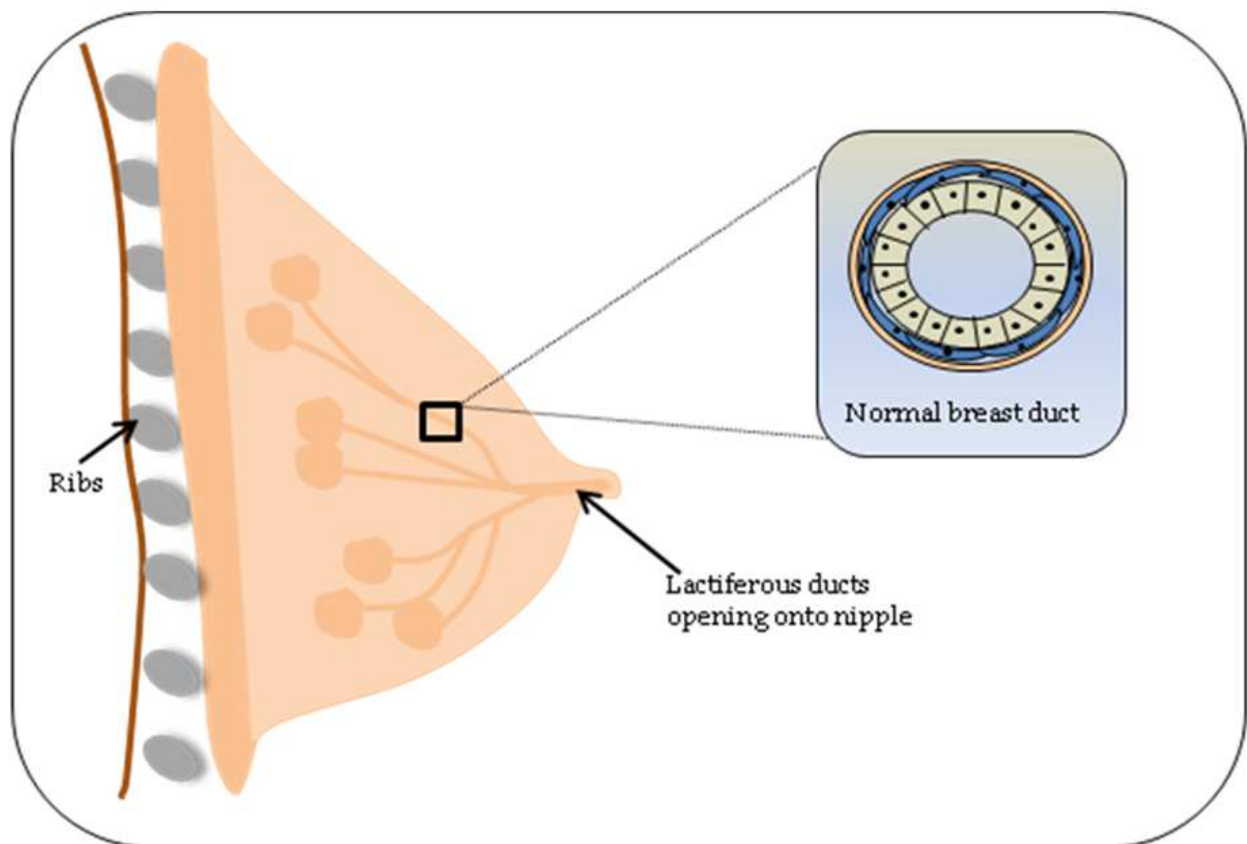

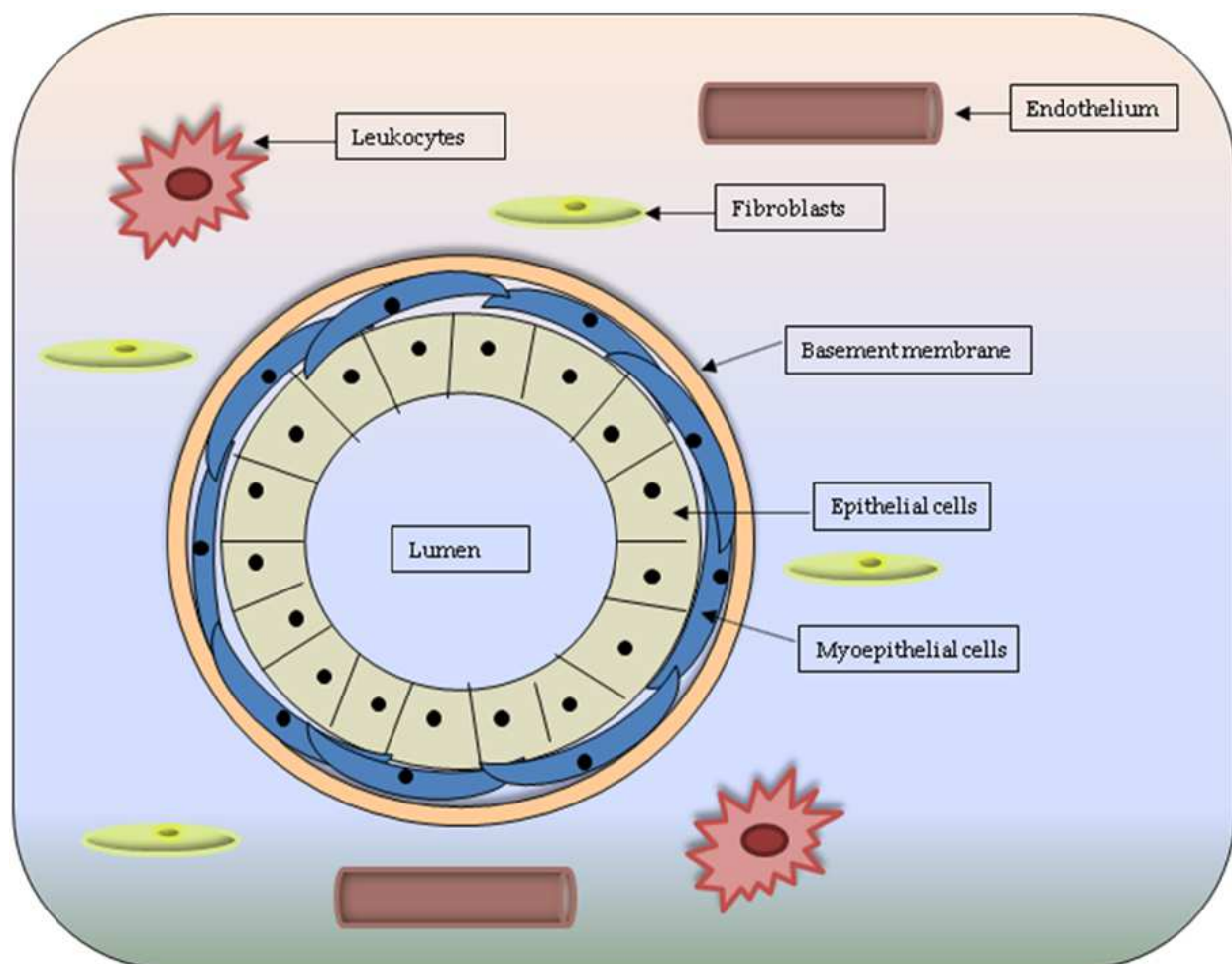Fig. 1. Structure of the breast showing lobules and lactiferous ducts terminating at the nipple

Fig. 2. Diagram of a normal breast duct depicting cells of the microenvironment.

1.2.1 Cells of the breast microenvironment

The abnormal epithelial cells composing a breast carcinoma form only one component of a complex microenvironment which influences the success or failure of a developing tumour. In fact the breast tumour microenvironment consists also of multiple cell types; including myoepithelial cells, fibroblasts, endothelial cells and immune cells such as macrophages (Figure 2). In terms of their likely contributions to breast tumourigenesis, fibroblasts and macrophages are often considered as tumour promoters through downstream signalling from various secreted factors, while the endothelial cells which develop in tumour-associated blood vessels also support cancer development. In contrast, myoepithelial cells exert functions broadly considered as tumour-suppressive.

Fibroblasts are an important structural component of the extracellular environment in the normal breast, where they help control the development of the breast epithelium (McCave *et al.* 2010). Their secretion of extracellular matrix components and cytokines has also implicated them in tumorigenic growth associated with invasive breast cancer (Orimo *et al.*, 2005), and differences in cellular responsiveness to normal versus tumour-derived fibroblasts have been noted (Sadlonova *et al.*, 2005). Many studies have highlighted the

potential involvement of fibroblasts in promoting tumour progression both at genomic and transcriptomic levels, with reports of altered genetic signatures between normal and tumour-associated fibroblasts supporting a complex role for fibroblasts in influencing tumour progression (Hu *et al.,* 2005; Hu *et al.,* 2008; Ma *et al.,* 2009).

Macrophages within the breast cancer microenvironment have been shown to enhance tumour growth through the secretion of pro-angiogenic factors like vascular endothelial growth factor (VEGF); (Murdoch *et al.,* 2004; Lamagna *et al.,* 2005 ; Lewis & Hughes, 2007). They have also been implicated in promoting a metastatic phenotype, via the secretion of pro-migratory factors such as EGF (Wyckoff *et al.,* 2004) which enhance cellular dissemination from a primary tumour. Accordingly, the enhanced physical juxtaposition of macrophages, tumour cells and endothelial cells has been proposed as a new prognostic histopathological marker associated with increased risk of metastases in human breast cancer (Robinson *et al.,* 2009).

Endothelial cells which line the blood vessels are derived from angioblasts forming the vascular network. Enhanced vessel density occurring as a result of tumour-associated angiogenesis is a major contributor to both the survival of primary breast tumours (via the delivery of systemic growth factors) and the risk of metastasis (via increased access of disseminated tumour cells to a circulatory source). Expression of pro-angiogenic factors such as VEGF has been shown to increase in haematological malignancies (Fiedler *et al.,* 1997; Molica *et al.,* 1999) in addition to solid tumours including breast, renal, ovarian, gastric and lung cancer (Patel *et al.,* 2009; Burger, 2011; Gou *et al.,* 2011; Sharma *et al.,* 2011). VEGF promotes neovascularisation via mitogenic and pro-migratory effects on endothelial cells (Asahara *et al.,* 1999).

Finally, myoepithelial cells are known to play a role in the formation of the basement membrane and thereby assist in maintaining polarity of the breast ductal epithelium. They also interact with epithelial cells to regulate the cell cycle and suppress breast cancer cell growth, invasion and angiogenesis (Weaver *et al.,* 1996; Alpaugh *et al.,* 2000; Barsky, 2003). Tumour and non-tumour primary myoepithelial cells have been described to differ in functional properties relating to the secretion of extracellular matrix components such as laminin-1 (Gudjonsson *et al.,* 2002), and accordingly myoepithelial cells reportedly lose their established tumour-suppressive properties during tumour progression (Polyak & Hu, 2005). Taken together, the many cell types within the breast tumour microenvironment can both individually and coordinately regulate several functions relevant to tumour progression. In order to better understand their relative contributions to breast cancer, it is necessary to dissect the signals that regulate their own functions. Since adhesive functions are central to the behaviour of all of these cell types, the remainder of this chapter will focus on their potential regulation by a family of adhesion proteins termed the Junction Adhesion Molecules (JAMs), whose role in breast cancer initiation and progression is just emerging.

2. Cell-cell adhesion and the functional roles of JAMs in epithelial/endothelial cells

2.1 Introduction to cell-cell adhesion complexes and JAMs

Cells within the breast tumour microenvironment physically interact with each other and with the extracellular matrix through a range of cell adhesion proteins. Cell adhesion proteins play fundamental roles in normal physiology (such as the control of cell polarity and epithelial barrier function), but their dysregulation has been shown to participate in

tumour cell migration, invasion and adhesion (for review, see Brennan *et al.*,2010). Adhesion proteins rarely exist in isolation from each other on the cell membrane, rather they form components of multi-cellular adhesion complexes containing a network of adhesion, scaffolding and signalling proteins. Breast epithelial cells express various types of adhesion complexes, namely hemidesmosomes and focal adhesions at the cell-matrix interface, with tight junctions, adherens junctions, desmosomes and gap junctions at the cell-cell interface. Collectively, adhesion complexes are composed of integral membrane proteins and cytoplasmic scaffolding proteins that organise signalling complexes and anchor cell-cell contacts to intermediate filaments (at desmosomes and hemidesmosomes) or to actin filaments (at adherens junctions, tight junctions and focal adhesions).

Tight junctions (TJs) play a vital role in regulating the paracellular flux of ions, small molecules and inflammatory cells as well as defining distinctly-polarized membrane domains and facilitating bi-directional signalling between the intracellular and extracellular compartments. These functions of the TJ are regulated by the balance of three different types of integral membrane proteins; (1) Occludins and Tricellulin, (2) Claudins and (3) Immunoglobulin Superfamily (IgSF) members. Of most interest in this chapter is the Junctional Adhesion Molecule (JAM) subfamily of the IgSF, and its potential contribution to cancer initiation and progression.

The JAM family consists of 5 proteins (JAM-A, -B, -C, -4, -L) which are major components of TJs in endothelial and epithelial cells in a variety of vertebrate and invertebrate tissues (Martin-Padura *et al.*, 1998; Liang *et al.*, 2000; Liu *et al.*, 2000; Arrate *et al.*, 2001; Aurrand-Lions *et al.*, 2001; Itoh *et al.*, 2001; Hirabayashi *et al.*, 2003; Tajima *et al.*, 2003). JAM proteins are also expressed on the surface of haematopoetic cells such as platelets, neutrophils, monocytes, lymphocytes, leukocytes and erythrocytes; in addition to connective tissue cells such as fibroblasts and smooth muscle cells (Azari *et al.*, 2010; Kornecki *et al.*, 1990; Naik *et al.*, 1995; Malergue *et al.*, 1998; Williams *et al.*, 1999; Cunningham *et al.*, 2000; Palmeri *et al.*, 2000; Arrate *et al.*, 2001; Aurrand-Lions *et al.*, 2001; Moog-Lutz *et al.*, 2003; Morris *et al.*, 2006). JAMs are type I transmembrane proteins consisting of an N-terminal signal peptide, an extracellular domain (consisting of two immunoglobulin-like domains), a single membrane-spanning domain and a short cytoplasmic tail (Martin-Padura *et al.*, 1998; Liu *et al.*, 2000; Sobocka *et al.*, 2000; Aurrand-Lions *et al.*, 2001; Naik *et al.*, 2001; Santoso *et al.*, 2002). The cytoplasmic tail is thought to play a major role in the assembly of adhesion signalling complexes, since it has been reported to bind to PDZ domain-containing scaffold proteins such as ZO-1 (Bazzoni *et al.*, 2000; Ebnet *et al.*, 2000), AF-6 (Ebnet *et al.*, 2000) and MUPP1 (Hamazaki *et al.*, 2002).

JAMs -A, -B and -C exhibit a short cytoplasmic tail of 45–50 residues that ends with a type II PDZ binding motif, while JAM-4 and JAM-L have longer cytoplasmic tails (of 105 and 98 residues respectively). JAM-4 and JAM-L differ in that the cytoplasmic tail of the former ends in a canonical type I PDZ binding motif, while that of the latter lacks a PDZ-binding motif (Mandell & Parkos, 2005). The cytoplasmic tails of JAM proteins also contain consensus phosphorylation sites that may serve as substrates for protein kinase C, protein kinase A and Casein Kinase II (Naik *et al.*, 1995; Cunningham *et al.*, 2000; Ozaki *et al.*, 2000; Sobocka *et al.*, 2000; Arrate *et al.*, 2001; Naik *et al.*, 2001). Indeed, evidence suggests that specific phosphorylation sites may be critical for targeting of JAMs to intercellular junctions (Ozaki *et al.*, 2000; Ebnet *et al.*, 2003).

JAM proteins have been implicated in a diverse array of physiological functions involving cell–cell adhesion/barrier function (Liang *et al.*, 2000; Liu *et al.*, 2000; Mandell *et al.*, 2004), leukocyte migration (Martin-Padura *et al.*, 1998; Palmeri *et al.*, 2000; Johnson-Leger *et al.*, 2002; Ostermann *et al.*, 2002), platelet activation (Kornecki *et al.*, 1990; Naik *et al.*, 1995; Gupta *et al.*, 2000; Ozaki *et al.*, 2000; Sobocka *et al.*, 2000; Naik *et al.*, 2001; Babinska *et al.*, 2002; Babinska *et al.*, 2002) and angiogenesis (Naik *et al.*, 2003; Naik *et al.*, 2003). These functions will be further discussed in the next sections.

2.2 JAM proteins regulate epithelial/endothelial cell–cell adhesion and barrier function

JAM proteins are well-known to be important for cell-cell adhesion in both epithelial and endothelial cells (for review see Mandell & Parkos, 2005), but emerging evidence supports the possibility that they also regulate cell-matrix adhesion complexes. Interestingly, JAM-A knockdown in endothelial cells and MCF7 breast cancer cells has been shown to reduce adhesion to fibronectin and vitronectin (McSherry *et al.*, 2011; Naik & Naik, 2006), while JAM-C overexpression in endothelial cells reportedly decreases attachment to fibronectin, vitronectin, and laminin (Li *et al.*, 2009). This apparent incongruity may relate to the fact that JAM-A may activate β1 integrins (McSherry *et al.*, 2011), while JAM-C has conversely been described to inactivate β1 integrins (Li *et al.*, 2009). An inverse relationship between JAMs – A and –C has also been observed in terms of tight junction function, with JAM-A promoting tight junction sealing while phosphorylated JAM-C increases paracellular leakiness due to its redistribution away from TJs (Li *et al.*, 2009). Furthermore, adhesion of the lung carcinoma cell line NCI-H522 to endothelial cells was significantly blocked by soluble JAM-C (Santoso *et al.*, 2005).

The contribution of JAM proteins to cell-cell adhesion and the assembly of epithelial/endothelial TJs relates to their ability to promote the localization of ZO-1, AF-6, CASK and occludin at points of cell-cell contact. Evidence suggests that both homophilic and heterophilic interactions, as well as an intact PDZ binding motif, are important for such protein functions of JAMs. Accordingly, JAMs have been shown to physically interact with the PDZ proteins, ZO-1 (Bazzoni *et al.*, 2000; Ebnet *et al.*, 2000), AF-6 (Ebnet *et al.*, 2000), CASK (Martinez-Estrada *et al.*, 2001), PAR-3 (Ebnet *et al.*, 2001; Itoh *et al.*, 2001) and MUPP-1 (Hamazaki *et al.*, 2002); which are involved in actin cytoskeletal rearrangement (Fanning *et al.*, 2002), cell signalling (McSherry *et al.*, 2011; Boettner *et al.*, 2000) and the control of cell polarity. However JAMs can also bind to non-PDZ proteins such as cingulin (Bazzoni *et al.*, 2000), and indirectly bind occludin (Bazzoni *et al.*, 2000) and claudin 1 via their interactions with ZO-1 (Hamazaki *et al.*, 2002). Although the manner in which JAMs interact with some of these proteins is incompletely understood, it appears that homo-dimerisation of JAM proteins is important for regulating some key downstream functions. This has been illustrated by the fact that dimerisation-blocking anti-JAM-A antibodies (Liu *et al.*, 2000) and soluble Fc–JAM-A (Liang *et al.*, 2000) delay the recovery of electrical resistance (a marker of TJ function) in epithelial cells following transient depletion of extracellular calcium.

2.3 JAM proteins regulate epithelial/endothelial migration

In general cell adhesion and cell migration are inversely related, and serve to control important physiological functions and pathophysiological events. However, in the case of JAM family members, close functional associations with cell polarity proteins may act as a switch between increased adhesion (predisposing to slow, directional migration) and decreased

adhesion (predisposing to faster, more random motility). For example, JAM-A re-expression in JAM-A-/- mouse endothelial cells has been shown to reduce the occurrence of spontaneous and random motility. This ability of JAM-A to influence the polarised movement of cells was reliant on its interaction with polarity proteins through its PDZ binding motif (Bazzoni & Dejana, 2004). JAM-A deletion mutants lacking their PDZ-binding residues have been shown to have increased availability of Par3 (Ebnet *et al.*, 2001), resulting in PKCζ inactivation and the loss of contact-dependent inhibition of cell motility (Mishima *et al.*, 2002; Bazzoni & Dejana, 2004). These data show that loss of functional JAM-A results in faster random motility with reduced cell-cell contact inhibition of migration. Interestingly, JAM-C redistribution away from TJs stimulates β1 and β3 integrin activation, resulting in increased cell migration and adhesion (Aurrand-Lions *et al.*, 2001). Furthermore, JAM-A and JAM-4 have been found to induce the formation of actin-based membrane protrusions, an essential part of cell migration, in endothelial and COS-7 cells (Mori *et al.*, 2004). Together these data suggest loss of JAM-A promotes random motility, while JAM-A, JAM-C and JAM-4 promote directional cell migration through their effects on integrin function and cytoskeletal reorganization.

In the context of cancer, knockdown of JAM-A has been shown to enhance invasiveness of the breast cancer cell lines MDA-MB-231 and T47D, and the renal cancer cell line RCC4 (Naik *et al.*, 2008; Gutwein *et al.*, 2009). Conversely, the overexpression of JAM-A in MDA-MB-231 cells reportedly inhibits both migration and invasion through collagen gels (Naik *et al.*, 2008), suggesting that loss of JAM-A expression increases cancer cell dissemination and invasion. However, the specific contribution of JAM-A to breast cancer progression remains controversial. McSherry *et al* showed a significant association between *high* JAM-A gene or protein expression and poor survival in 2 large cohorts of patients with invasive breast cancer, and concurrently a decrease in the migratory abilities of high JAM-A-expressing MCF-7 cells upon knockdown or functional inhibition of JAM-A (McSherry *et al.*, 2009). Reduced motility after JAM-A loss was subsequently linked to reduced interactions between JAM-A, AF-6 and the Rap1 activator PDZ-GEF2, resulting in reduced activity of Rap1 GTPase (McSherry *et al.*, 2011), a known activator of β1-integrins (Sebzda *et al.*, 2002) and a regulator of breast tumourigenesis (Itoh *et al.*, 2007). Complementary evidence in a recent publication by Gotte *et al.* has also supported the theory that JAM-A overexpression is of more functional relevance in breast cancer than JAM-A loss, since over-expression of micro RNA (miR)-145 in breast cancer cells led to a decrease in cellular migration and invasion via downregulation of JAM-A expression (Gotte *et al.*, 2010). Still more recently (during the proofing stage of this chapter), additional histopathological evidence has been provided for a link between JAM-A over-expression and poor prognosis in breast cancer patients (Murakami *et al.*, 2011). This, along with the finding that JAM-A promotes the survival of mammary cancer cells (Murakami *et al.*, 2011), strongly suggests that JAM-A depletion or antagonism could offer promise in reducing breast tumour progression. Furthermore, depletion of JAM-A has been found to inhibit bFGF-induced migration of human umbilical vein endothelial cells (HUVEC) on vitronectin, through effects on integrin function (Naik & Naik, 2006). In other cell systems, silencing of the JAM-A gene has been shown to block the migration of inflamed smooth muscle cells (Azari *et al.*, 2010) and to increase the random motility of dendritic cells (Cera *et al.*, 2004). JAM-A has also been shown to be required for neutrophil directional motility (Corada *et al.*, 2005), and to promote neutrophil chemotaxis by controlling integrin internalization and recycling (Cera *et al.*, 2009). Thus while the area remains controversial, increasing evidence is suggesting that JAMs promote migration and

invasion through the regulation of integrin expression and activation (McSherry *et al.*, 2011; Naik & Naik, 2006; Li *et al.*, 2009; McSherry *et al.*, 2009).

In breast cancer, the formation of metastases at distant sites is the leading cause of cancer-related death. In order for breast cancer cells to metastasize, they must first migrate out of the primary tumour before ever reaching a distant organ and potentially proliferating into a secondary tumour. While JAMs are already known to regulate migration, the possibility that they are also involved in the regulation of proliferation will be referred to in section 3.3 of this chapter.

All together these data highlight the role of JAM family members in controlling the balance between cell adhesion and migration. Although much remains to be understood about the exact role of JAMs in breast cancer cell migration, the classic description of tumours as "wounds which do not heal" (Riss *et al.*, 2006) suggests that the migratory mechanisms employed by JAMs in physiological responses (such as wound healing) may also be utilised by cancer cells to promote tumour progression or survival.

2.4 Potential role of JAM proteins in epithelial/endothelial differentiation

In previous sections we discussed the biphasic role of JAM family members in regulating cell adhesion and migration. In this section we will outline the emerging contribution of the JAM family to cellular differentiation. Cell differentiation in the context of normal tissue usually involves the transition from an undifferentiated stem/progenitor cell to a terminally-differentiated cell such as an epithelial, muscle or nerve cell.

JAM-A, JAM-B, JAM-C and JAM-4 have been found to be highly expressed on hematopoietic stem cells (HSCs) in the bone marrow, with their expression decreasing during the acquisition of a more differentiated state (Nagamatsu *et al.*, 2006; Sakaguchi *et al.*, 2006; Sugano *et al.*, 2008; Praetor *et al.*, 2009). Furthermore JAM-A expression has been reported to be high on undifferentiated HC11 mammary epithelial cells relative to differentiated cells (Perotti *et al.*, 2009). In support of a potential association between high JAM-A and poor differentiation status, high JAM-A gene or protein expression has been associated with a poorer grade of differentiation in tissues from patients with invasive breast cancer (McSherry *et al.*, 2009). Conversely, JAM-A has been found to mediate the differentiation of CD34+ progenitor cells to endothelial progenitor cells and to facilitate CD34+ cell-induced re-endothelialization *in vitro* (Stellos *et al.*, 2010). This suggests that JAM-A is required for circulating CD34+ progenitor cells to recognise a site of injury, differentiate into endothelial cells and proliferate to repair the injured endothelium. In addition, JAM-A is reportedly upregulated during the differentiation of pancreatic AR42J cells (Yoshikumi *et al.*, 2008), while JAM-A mRNA and protein levels have been shown to be increased during differentiation of human monocytic cell THP-1 into mature dendritic cells (Ogasawara *et al.*, 2009). JAM-L is also induced during differentiation of myeloid leukaemia cells, with expression of JAM-L in myeloid leukaemia cells resulting in enhanced cell adhesion to endothelial cells (Moog-Lutz *et al.*, 2003). This upregulation of JAM-A during differentiation is reportedly followed by increased expression of the polarity proteins par3 and PKCλ (Yoshikumi *et al.*, 2008), which have been previously shown to affect cell polarity and migration. While these data suggest conflicting roles for JAMs in stem cell populations versus their role in differentiation, at this early stage the exact role(s) of JAMs in stem cell renewal or differentiation can only be speculated upon. Fundamentally, it is also unknown whether the expression of JAMs is actively required or

passively upregulated in stem cell populations. However, based on the increased expression of JAM-A in poorly-differentiated breast cancers (McSherry *et al.*, 2009) and the emerging role of JAM-A in regulating proliferation and apoptosis (Azari *et al.*, 2010; Nava *et al.*, 2011; Naik *et al.*, 2003; Murakami *et al.*, 2011), it will be interesting to determine if JAM-A is upregulated on cancer stem cell populations and whether its expression promotes self-renewal.

3. Functional regulation of cells in the breast cancer microenvironment by JAMs

3.1 JAM proteins regulate endothelial angiogenesis

As already alluded to, JAM proteins are highly expressed on endothelial cells and have been crucially implicated in the control of barrier function and cell motility. In the context of cancer, however, endothelial cells assume a new importance via the development of neovascularisation sites to support growing tumours (Hanahan & Folkman, 1996). This section will review the evidence currently linking JAM proteins to angiogenesis as a contributory mechanism to cancer progression.

Angiogenesis in response to enhanced growth factor signalling is of particular relevance in tumour microenvironments. A body of work from Naik *et al* has convincingly shown an important role for JAM-A in angiogenesis induced by basic fibroblast growth factor (bFGF). Specifically, bFGF signalling facilitates the disassembly of an inhibitory complex between JAM-A and αvβ3 integrin, permitting JAM-A-dependent activation of MAP kinase which leads to endothelial tube formation, a surrogate for angiogenesis (Naik *et al.*, 2003). JAM-A has also been shown to activate extracellular signal-related kinase (ERK) signalling in response to bFGF, facilitating endothelial migration (Naik *et al.*, 2003) in a matrix-specific context (Naik & Naik, 2006). *In vivo*, JAM-A expression has been linked with the very early stages of murine embryonic vasculature development (Parris *et al.*, 2005), and although deletion of JAM-A appears to be dispensable for vascular tree development, homozygous JAM-null mice were found to be incapable of supporting FGF-2-induced angiogenesis in isolated aortic ring assays (Cooke *et al.*, 2006). In the context of tumour neovascularisation, others have reported reduced angiogenesis in a model of pancreatic carcinoma in JAM-A-null mice (Murakami *et al.*, 2010).

Other JAM family members appear to contribute similarly to angiogenesis; with functional blockade of JAM-C being shown to decrease aortic ring angiogenesis and block angiogenesis in hypoxic vessels of the murine retina (Lamagna *et al.*, 2005; Orlova *et al.*, 2006). Furthermore, soluble JAM-C shed into the serum of patients with inflammatory conditions (presumably following cleavage by ADAM enzymes) was noted to induce endothelial tube formation in a Matrigel model (Rabquer *et al.*, 2010). An interesting dichotomy, however, is that amplification of JAM-B in a trisomy-21 mouse model of Down's syndrome has been linked with reductions in VEGF-induced angiogenesis and thus anti-tumour effects in a lung carcinoma model in these mice (Reynolds *et al.*, 2010).

Taken together, these studies illustrate that by influencing angiogenic functions in endothelial cells, JAMs may indirectly influence the ability of tumours to survive and progress. While there appears to be a consensus that JAMs –A and –C activate signalling cascades that promote angiogenesis, it is possible that clear roles for the other family members in the regulation of angiogenesis will also emerge in time. It is tempting to speculate that pharmacological antagonism of JAMs will show promise as an option for

blocking tumour progression, similar to the VEGF-A-neutralizing antibody bevacizumab (avastin) (Van Meter & Kim, 2010).

3.2 JAM proteins regulate trafficking of leukocytes

In addition to the potential regulatory roles of JAM proteins on the vascular endothelium, effects exerted on JAM-expressing leukocytes within the breast tumour microenvironment may also have relevance to cancer progression. For instance, JAMs are known to play important roles in the transendothelial migration of monocytes, which differentiate into macrophages once in the breast tissue. Accordingly, a function-blocking monoclonal antibody directed against JAM-A (BV11) has been described to inhibit spontaneous and chemokine-induced monocyte transmigration both *in vitro* and *in vivo* (Martin-Padura *et al.*, 1998). Furthermore, treatment of mice with a monoclonal antibody directed against JAM-C has been shown to reduce macrophage infiltration into a murine lung tumour model (Lamagna *et al.*, 2005), and to promote reverse transmigration of monocytes back into the bloodstream from inflamed tissue sites (Bradfield *et al.*, 2007). Given the existence of a breast tumour-promoting paracrine loop between epidermal growth factor secreted by macrophages and colony-stimulating factor-1 secreted by tumour cells (Goswami *et al.*, 2005), this implies that JAM-based regulation of monocyte transmigration could have a profound and self-amplifying influence on macrophage trafficking and tumour proliferation.

In the context of leukocytes other than monocytes/macrophages, many studies have implicated JAMs in the functional control of neutrophil transmigration across both epithelial (Zen *et al.*, 2004; Zen *et al.*, 2005) and endothelial (Sircar *et al.*, 2007; Woodfin *et al.*, 2007) barriers. As yet nothing is known about JAM-dependent events that might control neutrophil trafficking or activation within the breast tissue, despite the fact that neutrophils accumulate in highly aggressive inflammatory breast cancers. In other tissues, JAM-A has been shown to be required for efficient infiltration of neutrophils into the inflamed peritoneum or into the heart upon ischemia–reperfusion injury; as evidenced by increased adhesion and impaired transmigration in JAM-A-deficient mice (Corada *et al.*, 2005). Interestingly, in this model JAM-A expression on the neutrophil appears to be more important than that on the endothelium; since selective loss of endothelial JAM-A did not phenocopy the transmigration deficits (Corada *et al.*, 2005). In addition, soluble JAM-A shed from cultured endothelial cells has been shown to reduce *in vitro* transendothelial migration of neutrophils and to decrease neutrophil infiltration *in vivo* (Koenen *et al.*, 2009).

Recent evidence also proves that family members other than JAM-A can participate in leukocyte trafficking, with JAM-C over-expressing mice exhibiting an increased accumulation of leukocytes into inflammatory sites or during ischaemia/reperfusion injury, while JAM-C neutralization or loss reduces leukocyte recruitment in models of lung, kidney or muscular inflammation (Aurrand-Lions *et al.*, 2005; Scheiermann *et al.*, 2009). Finally leukocytic expression of JAM-L has been shown to promote attachment to endothelium (Luissint *et al.*, 2008), and functional inhibition of JAM-B is reported to decrease migration of peripheral blood lymphocytes across cultured human umbilical vein endothelial cells (HUVECs) (Johnson-Leger *et al.*, 2002).

Collectively these data highlight an important role for JAMs in the migration of immune cells across endothelia, a mechanism that could be hijacked by JAM-overexpressing cancer cells as they leave the breast and invade into blood vessels.

3.3 JAM proteins and the regulation of stromal cells

The final grouping of breast cancer microenvironmental cells which will be discussed are stromal cells, broadly including fibroblasts and myoepithelial cells. Although little is known about JAM-mediated control of breast stromal cells specifically, insights from other cellular systems may suggest that this multifunctional family of proteins could have a hand in influencing the mesenchymal element of tumourigenic processes.

JAM-C expression has been noted on the surface of primary fibroblasts derived from human lung, skin and cornea (Morris *et al.*, 2006). The same authors observed JAM-A and JAM-C expression on the widely-studied NIH-3T3 fibroblast cell line. Interestingly, high JAM-C expression on synovial fibroblasts has been associated with the pathology of murine experimental arthritis, and JAM-C antagonism shown to have functional benefits in reducing the severity of inflammation (Palmer *et al.*, 2007). An immunohistochemical study in human arthritis has also demonstrated JAM-C expression on the synovial fibroblasts of both osteoarthritis and rheumatoid arthritis patients, in conjunction with JAM-C-dependent adhesion of myeloid cells to these fibroblasts (Rabquer *et al.*, 2008). Enhanced expression of JAM-A has also been described on the skin of patients with the inflammatory disorder systemic sclerosis, in comparison to that on normal dermal fibroblasts (Hou *et al.*, 2009).

Aside from facilitating adhesion of leukocytic cells to stromal elements such as fibroblasts, another way in which JAM family members could influence the breast cancer microenvironment is by altering proliferation of fibroblasts or other accessory cells. JAM-A has been reported to be required for proliferation of vascular smooth muscle cells, since JAM-A gene silencing exerted anti-proliferative effects in this system (Azari *et al.*, 2010). Whether this is through direct or indirect mechanisms remains uncertain, particularly in light of conflicting evidence in intestinal epithelial cells suggesting that JAM-A expression restricts proliferation by inhibiting Akt-dependent Wnt signalling (Nava *et al.*, 2011). However functional inhibition of the extracellular domain of JAM-A has been shown to inhibit bFGF-induced endothelial cell proliferation, and overexpression of JAM-A was also found to increase endothelial cell proliferation (Naik *et al.*, 2003). Accordingly, very recent evidence has suggested that JAM-A expression exerts a negative tone on apoptosis in the mammary epithelium (Murakami *et al.*, 2011). It is likely that processes as crucial as proliferation are strictly regulated in a spatial manner, which could account for tissue-specific differences as observed from the little available evidence to date. Whether or not JAM family members may influence proliferation of breast stromal cells like fibroblasts and the myoepithelium remains to be investigated. However, it is tempting to speculate that the acquisition of a proliferative phenotype in tumours may be co-ordinately linked to the pro-migratory "mesenchymal" phenotypes observed in many aggressive, poorly-differentiated breast cancers, to which evidence has already linked members of the JAM family. Co-culture models which better recapitulate the complexity of the breast cancer microenvironment than mono-cultures (Holliday *et al.*, 2009) may offer promise in dissecting the relative cellular contributions of JAMs to tumour progression at a reductionist level.

4. JAMs as novel potential drug targets in breast cancer

The pleiotrophic roles of JAM family members in regulating both the breast epithelium and cells of the microenvironment may suggest JAMs as novel therapeutic targets for the future management of breast cancer. Whether by aiming to block migratory behaviour, angiogenesis, proliferation or to promote polarisation and differentiation, selective

pharmacological targeting of JAM molecules could prove particularly useful in cancers that overexpress one or more JAMs. This naturally pre-supposes that JAMs are causally involved in the disease process rather than simply acting as passive biomarkers, a fact that remains to be solidified. However, irrespective of the last caveat, another facet worth exploring is the potential of targeting JAMs to promote drug delivery. Since tight junctions (TJs) as a whole are primary regulators of paracellular transport across epithelial cells (Gonzalez-Mariscal *et al.*, 2005), successful drug delivery may require modulation of TJ proteins to allow drug molecules to pass (Matsuhisa *et al.*, 2009). However disruption of TJ proteins for drug delivery purposes is a double-edged sword, given the risk of disrupting homeostatic mechanisms of polarity, differentiation and migration which are tightly regulated by TJs in normal tissues and whose dysregulation may themselves promote tumourigenesis.

As yet, there are no cancer therapies on the market which specifically target tight junctions. However several tight junction proteins have been described as receptors for specific molecules or organisms, and as such, these might provide valid and novel targets for drug delivery. A particular precedent exists with the claudin family of TJ proteins; Claudins-3 and -4 having been suggested as drug delivery targets since they act as the receptor for *Clostridium perfringens* enterotoxin (CPE). The ability of CPE to rapidly and specifically lyse cells expressing claudin-3 or -4 could potentially be exploited in the treatment of breast cancers over-expressing these proteins (Katahira *et al.*, 1997; Morin, 2005; Santin *et al.*, 2007; Santin *et al.*, 2007). Sub-lytic doses of CPE could alternatively be used to compromise TJs thus enhancing the influx of drug molecules across the epithelium. This could be of particular benefit in accessing hypoxic tumour cores, around which the tumour cells may be very tightly packed and thus relatively inaccessible to chemotherapeutic drugs. To date CPE administration has been shown to reduce growth of claudin-4 overexpressing pancreatic tumour cells (Michl *et al.*, 2001; Michl *et al.*, 2003), but their potential use in other cancer settings remains an open question.

How JAM molecules might be therapeutically targeted also remains an unanswered question, but one could predict value in using monoclonal antibodies or small molecule inhibitors to block the signalling functions which contribute to processes such as migration and angiogenesis. However, to date, the role of JAMs as chemotherapeutic targets (or even prognostic/predictive biomarkers) in the clinical setting of breast cancer has yet to be elucidated and validated. Following the lead of JAM-A as a potential biomarker and therapeutic target for breast cancer (McSherry *et al.*, 2009; Gotte *et al.*, 2010; McSherry *et al.*, 2011; Murakami *et al.*, 2011), we speculate that this will be a lucrative area of research in the future.

5. Conclusion

To conclude, breast cancer remains a leading cause of cancer worldwide (Jemal *et al.*, 2008), and the search for new targets of prognostic and therapeutic relevance will continue particularly in this era where semi-personalised medicine is becoming more of a likelihood than an aspiration.

This chapter has attempted to summarize the known roles of the JAM family in controlling cell adhesion, polarity and barrier function, and their emerging roles in controlling functional behaviours within cells of the breast tumour microenvironment which promote cancer progression. Finally, it introduced the topic of JAM as a potential drug target in breast cancer; whether to directly influence JAM-dependent oncogenic signalling or indeed to interfere with cell-cell adhesion for the purposes of enhancing drug delivery. Continued

expansion in our understanding of the cell and molecular biology of JAMs and their roles in tumour progression may open up new horizons supporting their evaluation as breast cancer biomarkers and drug targets of the future.

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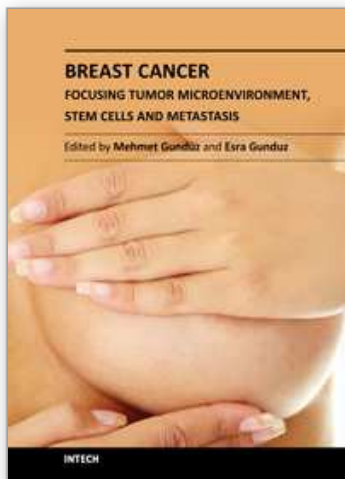
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Edited by Prof. Mehmet Gunduz

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