The role of matrix metalloproteinases in cancer progression, in particular metastasis

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Abstract

Cancer is a major global health concern, and is one of the leading causes of mortality in many developed countries including Australia. Most of the morbidity and mortality associated with cancer can be linked to the process of metastasis, whereby malignant cancerous cells move from their primary site to establish secondary tumours at a distant location. The capacity of cells to migrate through a tissue depends on their ability to degrade the extracellular matrix. Matrix metalloproteinases are the main protease enzymes involved in the degradation of the extracellular matrix. The release of these enzymes is important, not just for normal immune and inflammatory processes, but also for cancer.

Key words: cancer, metastasis, inflammation, matrix metalloproteinases, substance P.

Introduction

Cancer is a major problem worldwide, and is the leading cause of mortality in Australia [1]. Particularly in countries with aging populations, there is a potential for further increases in its incidence worldwide [2, 3]. Cancer is not only a cause of mortality, but it also has negative effects on quality of life, family relationships, functional status, and social functioning. In addition, it has a range of economic impacts, including health care costs, employability, productivity, and insurability [4].

The term neoplasm or (tumour) refers to a new growth or abnormal mass of tissue which does not obey the growth laws of a normal cell [5]. As such, they are characterized by progressive or uncontrolled proliferation of cells [6].

Neoplasms may be classified as benign or malignant. Benign neoplasms grow slowly, are enclosed in a fibrous capsule, are limited to a specific location, and are considered as non-cancerous [7]. Importantly, they do not cause death unless their location interferes with or affects vital body function [8].

By contrast, malignant neoplasms have lost the ability to control both cell proliferation and differentiation [9]. They are often fatal because the cancer cells can spread to distant sites through the bloodstream, lymphatic system, or through body spaces [10–17]. Moreover, cancer metastasis is the major reason for the failure of treatment, as well as the leading cause of mortality in individuals with malignant tumours [14, 18].

Thus, understanding the process by which tumour cells develop heterogeneity, invade local tissues, and spread to distant tissues is a major

goal of cancer research. An improved understanding of the metastatic process may enable the development of more effective therapies for a variety of different cancers.

Metastasis

It is the dissemination and implantation of cancer cells at metastatic sites that has been considered the final stage in a deteriorating process, and it is the major feature of malignant tumours, which are responsible for 90% of cancer-related deaths [19]. Metastasis is the movement of tumour cells to a site that is distant from the primary tumour and the adaption to create a favourable site for tumour growth involving the interaction between tumour cells and the host microenvironment. This is governed by the same factors that directed proliferation at the primary site [13, 14, 20, 21].

The implantation of tumours at secondary sites is not merely a random process. Rather, a "seed and soil" guided event is proposed. The organ-preference patterns of tumour metastasis are the product of favourable interactions between metastatic tumour cells (the "seed") and their organ microenvironment (the "soil") [22–24].

The spread of cancer cells may happen by penetration of the bloodstream, lymphatic tissue or via spaces surrounding organs [25–27]. As with benign neoplasms, malignant tumours arise because of cancer cells lacking the ability to balance cell division and cell death (apoptosis) [10, 12].

Additionally, they possess a variety of other characteristics that contribute to their metastatic potential. One of the critical first steps is that these transformed cells lose the ability to communicate and to interact with each other, which enables them to penetrate neighbouring tissues (invasion) before spreading via the bloodstream, or lymphatic system to distant sites [4, 28, 29]. Also, they can form their own new vascular supply from pre-existing vessels through the process of angiogenesis [30, 31].

Invasion is certainly a prerequisite for metastasis. In other words, without invasion there would be no metastasis [32]. Invasion usually happens before metastasis, with the tumour cells infiltrating the surrounding tissues before spreading to distant locations [16, 27, 33]. Furthermore, most cancer cells secrete proteases which enable them to break down the extracellular matrix of the surrounding tissue and thus facilitate the processes of invasion and metastasis [34–36].

Key points:
- Metastasis is responsible for 90% of cancer-related deaths.
- Metastasis is "seed and soil" guided event through interconnected stages.
- The cancer cells possess a variety of characteristics that contribute to their metastatic potential.

- Metastatic cells at a secondary site are governed by the same factors that directed proliferation at the primary site.
- Invasion is certainly a prerequisite for metastasis.
- Most cancer cells secrete proteases that are involved in the process.

Mechanisms associated with metastasis

All the stages of the metastatic process are complicated, and all are necessary for successful dissemination and implantation of the tumour in the secondary site [37]. The failure of completion of any stage entails the collapse of the overall process [37, 38]. In addition, it is not necessary that all the steps of the metastatic stages happen in a linear way; for example, premalignant tumours can already be vascularized, while the timing of induction of the pre-metastatic niche remains elusive [39]. One key point in the formation of metastases is that the cancer cells twice must cross the endothelial cells that line blood vessels (once during intravasation and once during extravasation) [17].

Moreover, cancer cell extravasation usually occurs in small capillaries, where the cells can be physically trapped by size restriction and can then form stable attachments to endothelial cells [17, 40].

Furthermore, in metastasis, many pairs of ligand–receptor molecules participate in the metastatic process, including cadherins, integrins, selectins, CD44 and immuno-globulin superfamily receptors [17].
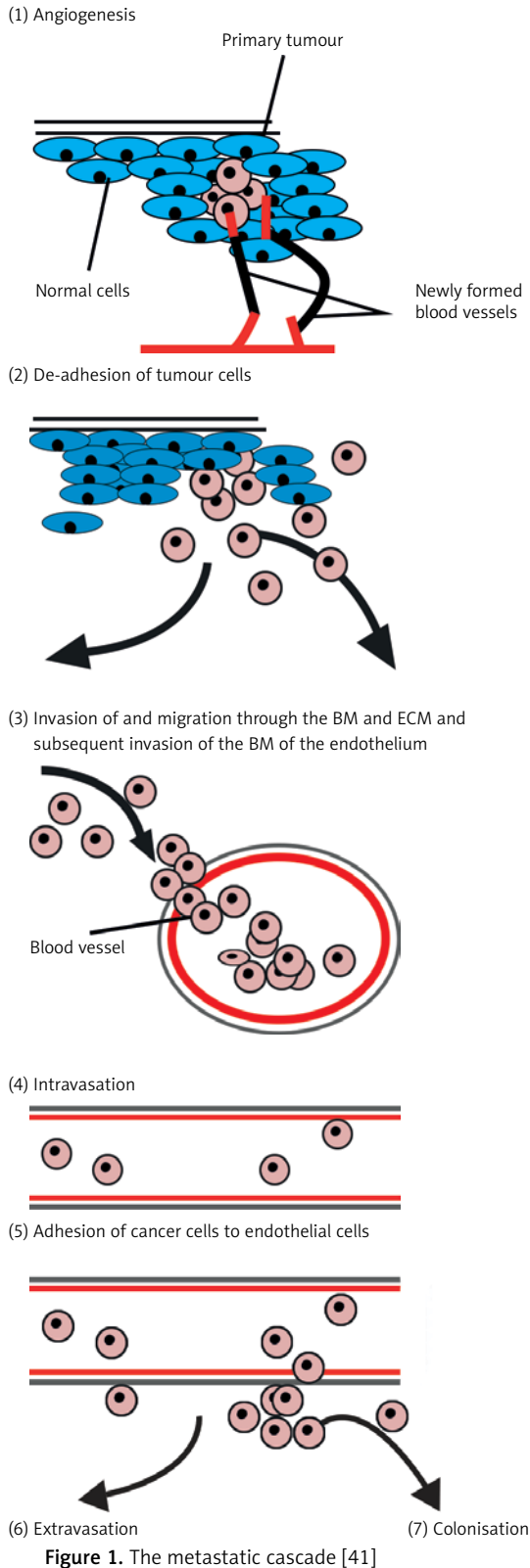
The metastatic cascade

Metastasis is often described as a 'cascade' of events, because there are multiple steps, which are interconnected, including a series of adhesive interactions and invasive processes, as well as responses to chemotactic stimuli [41].

In this section, we will provide a review of the stages involved in this process, with a focus on the extravasation step, and its significance in cancer metastasis. In addition, we will consider the mediators, the key molecules and molecular interactions involved in the complex cascade of events that lead to cancer cell metastasis.

The complex sequential manner of the metastatic cascade [39] can be summarized as follows (Figure 1) [41]:

Tumour angiogenesis

Formation of new blood vessels from pre-existing vasculature (angiogenesis) is required for the growth and metastasis of all solid tumours [42], and is a highly regulated process [43]. Moreover, angiogenesis is a significant biological process as

(1) Angiogenesis

Primary tumour

Normal cells

Newly formed
blood vessels

(2) De-adhesion of tumour cells

(3) Invasion of and migration through the BM and ECM and
subsequent invasion of the BM of the endothelium

Blood vessel

(4) Intravasation

(5) Adhesion of cancer cells to endothelial cells

(6) Extravasation   (7) Colonisation

Figure 1. The metastatic cascade [41]

part of growth and development [44], as well as
pathological processes including cancer and dif-
ferent types of diseases [42]. Currently, it is well
accepted that metastatic cancer could not prog-
ress without the formation of a blood supply to
the solid primary tumour mass [41]. Additional-

ly, tumour angiogenesis is one key factor in the
dissemination of cancer due to the metabolic de-
mands of tumour tissue being met through neo-
vascularization [45, 46].

Angiogenesis consists of a series of steps, and
depends on the balance between different mole-
cules released by the host and tumour cells [47,
48]. When the primary vascular plexus is formed,
more endothelial cells (ECs) are separated, which
can form new capillaries by sprouting or by split-
ting from their vessel of origin in a process termed
angiogenesis [49].

To stimulate angiogenesis, tumour cells and
surrounding stromal cells produce soluble pro-in-
flammatory and pro-angiogenic cytokines, such as
tumour necrosis factor α (TNF-α), vascular endo-
thelial growth factor (VEGF) and interleukin-8 (IL-8),
which diffuse into the nearby tissues and encoun-
ter pre-existing blood vessels near the tumour [49].
Additionally, they bind to receptors located on the
endothelial cells lining these blood vessels, and
on the tumour cells themselves, and stimulate the
production of adhesion molecules, including integ-
rins [48], proteases such as the matrix metallopro-
teinases (MMPs) and plasminogen activators [41].

Many stimulators of angiogenesis have been
identified, including the members of angiopoi-
etins, platelet-derived growth factor, and members
of the fibroblast growth factor (FGF) family [50]. In
addition, factors that control angiogenesis include
soluble growth factors, membrane-bound proteins,
cell–matrix and cell–cell interactions, and many in-
teracting systems [49]. Thus, targeting these fac-
tors, as well as adhesion molecules involved in the
mechanism of angiogenesis, represents an attrac-
tive approach for cancer treatment.

Disaggregation of tumour cells from the primary tumour

Detachment of cancer cells from each other,
and from the primary tumour, is the first stage
in metastasis for cancerous cells to initiate their
dissemination [41]. They lose their tight adhesion
with the neighbouring tissue, and then change
into a more invasive form, which is more mobile
and can degrade any hindering structure in their
way to access the blood vessels [51].

E-cadherins, mediators of cell-cell interactions,
play a crucial role in epithelial cell adhesion and in
the maintenance of tissue architecture [52]. In ad-
dition, cadherin molecules that are responsible for
intercellular adhesion expression were found to
be significantly reduced in some types of cancer
associated with metastatic phenotype [53].

Also, E-cadherin mediators have a prognostic
role, and could be a useful biomarker in the prog-
nosis or predication of cancer outcome [54, 55].
Furthermore, an association between down-regu-

lation of E-cadherin expression and a strong invasive potential has also been reported *in vivo* in cancers of the breast [56], nasopharynx [57], gastrointestinal tract [58], pancreas [59], lung [60], and kidney [61].

In addition to E-cadherin's role in cell adhesion, cadherin–catenin complexes are also involved in intracellular signal transduction pathways [62]. This interaction between cell adhesion and signalling functions might contribute to the mutual regulation of the cadherin–catenin complex [41].

Another adhesion molecule, N-cadherin, was shown to exist in the most invasive and dedifferentiated breast cancer cell lines. Its expression in tumour cells induces a varied morphology and heightened movement, invasion, and metastasis potential of the cells [52].

Moreover, there is a connection between N-cadherin and fibroblast growth factor (FGF) receptor, resulting in signals that lead to the regulation of MMP-9 [63]. In addition to a signalling function in metastasis, N-cadherin probably supports the systemic dissemination of tumour cells by enabling circulating tumour cells to connect with the stroma and the endothelium at distant sites [52, 63].

After separation of the cancerous cells from the primary tumour, they attach to matrix components which consist of collagens, proteoglycans and glycoproteins. Further, the breaking down of the basement membranes, and remodelling of the extracellular matrix (ECM) by proteinases, facilitates intravasation of these metastatic cells into lymph or blood vessels [17, 40].

Invasion of and migration through the basement membrane and ECM

Invasion and migration of cancerous cells through the basement membrane (BM) and ECM before getting inside blood vessels, is mediated by integrins and proteases, including urokinase form of plasminogen activator (uPA), MMPs and cathepsins [41, 64].

Intravasation of tumour cells into the blood vessels

Access of tumour cells to blood vessels prior to haematogenous dissemination to distant sites [64] might be affected by the specific characteristics of the blood vessels at which the intravasation occurs [64].

Studies on cancer cell intravasation have demonstrated that tumour cells are able to mechanically translocate and squeeze into the endothelial barrier by acquiring a migratory behaviour [65]. This includes the ability to orient themselves toward the blood vessels, change their shape into a more rounded form, and develop migratory pro-cesses that permit their movement [66]. Additionally, several factors for this mobility transformation have been identified, such as insulin growth factors and extracellular matrix molecules such as laminin and fibronectin [67].

Many integrins mediate tumour cell migration and invasion of the BM and its ECM [41]. For example, over-expression of α3β1 integrin by tumour cells contributes to the tumour cell invasion [41]. In addition, VEGF was identified as accompanying tumour associated angiogenesis, causing the formation of leaky vessels which provide easy access for intravasated cells [68].

The intravasation process could be active due to the release of chemotactic peptides and the movement of cells according to this gradient [69]. This active migration has been postulated to be a result of the ability of cancer cells to mimic some aspects of lymphocyte behaviour [69]. On the other hand, there is evidence supporting the hypothesis that intravasation is a passive mechanism. It has been postulated that the mechanical stress in the tumour overgrowth breaks the fragile, newly formed immature vessels, and pushes the tumour cells through these frail and weak barriers [69].

After the intravasation process, adhesion of the circulating tumour cells to the endothelial cell lining at the capillary bed takes place prior to extravasation and haematogenous dissemination to distant sites [70]. This occurs through adhesive interactions between cancer cells and endothelial cells involving selectins, integrins and members of the immunoglobulin superfamily (IgSF) [41, 70].

Adhesion of cancer cells to the endothelial cells

The adhesion of a circulating cancer cell to the microvasculature endothelium is a critical step in the extravasation stage, and the subsequent colonization. Cancer cells interact with many other circulating cells in the bloodstream, including platelets, monocytes, neutrophils and natural killer cells [71]. These cells can modulate the efficiency and capacity of cancerous cells for extravasation into established metastatic foci [71]. Therefore, the ability of tumour cells to form a metastatic colony correlates with their capacity to interact with and migrate through endothelial cell layers. This process involves multiple adhesive interactions between tumour cells and the endothelium [72].

Extravasation

Extravasation of cancer cells is the exit or the movement of cells out of the blood vessels or the lymphatic vessels through the endothelial cell layer, surrounding basement membrane (BM) and target organ tissue (Figure 2) [73].
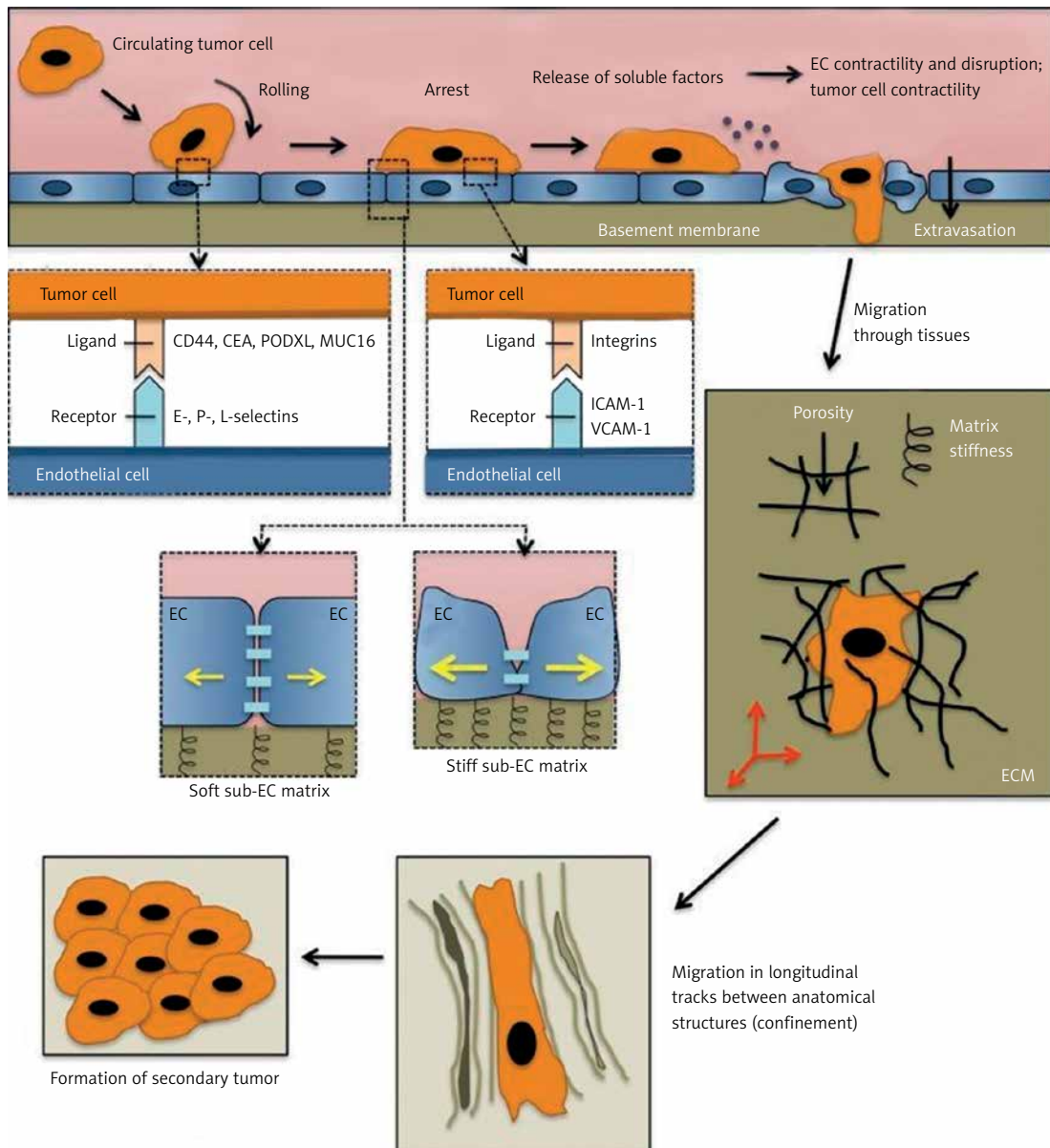
Figure 2. Stages of tumour cell extravasation [73]

It has been considered that cancer cell extravasation is the significant stage in cancer cell dissemination and implantation because adhesion, and eventually extravasation, are essential initial interactions of circulating tumour cells with distant organs [74]. In addition, cancer cells are enabled to escape from the cytotoxic environment within the circulation [74]. Indeed, the microenvironment within the circulation provides a variety not only of pro-metastatic stimuli, but also anti-metastatic stimuli that regulate the onset of organ colonisation by metastatic tumour cells [74, 75].

Migration of cancer cells throughout the body is not enough to cause distant tumours, because the cells should not be capable of surviving within environmental conditions which are totally different from those of their tissue of origin [76]. For example, blood and lymph, which are the main pathways for the spread of cancer cells, are hostile environments for cells not adapted to surviving in that environment [76, 77]. It was estimated that only about 1% of cancer cells that enter the circulation can survive to form secondary tumours [78, 79].

Additionally, when the cancer cell gets in the blood circulation, it will face several stresses that reduce the chances of its survival, including the fast-flowing blood, immune response attacks by white blood cell antibodies, and apoptosis signals induced by loss of cell contact, as well as rocking of cells against the wall of blood vessels [80, 81]. Furthermore, blood serum contains waste products and other substances that are toxic to cancer cells [27].

The extravasation process is in principle divided into three sequential steps: rolling, adhesion, and transmigration (diapedesis) [51].

The first step (rolling): The initial interactions of cancer cells with the vascular endothelial cells are weak [17]. Due to this loose attachment, the extravasating cells are pulled along with the bloodstream, which results in a rolling movement of the cells on the vascular surface [51].

Cancer cell interactions with endothelial cells are mediated by E-selectin, a significant element for metastasis [82, 83]. E-selectin has been shown to be up- regulated in endothelial cells at the site of liver metastasis [84]. In addition, media from cancer lines had induced expression of E-selectin when added to endothelial culture [82, 84, 85]. Moreover, it has been revealed that cancer cells with high expression of the selectin ligands bind more efficiently and extravasate at higher rates than those with low expression [86].

It has been found that the same mechanisms are involved in the interaction of leukocytes with endothelial cells [87, 88]. Also, leukocytes act as bridge or linker cells to facilitate the contact between tumour cells and the endothelium [89].

Further, it has been indicated that the tumour cells lack β_2-integrins, which are the ligand for the intercellular adhesion molecule (ICAM-1) on the endothelium. Instead, the tumour cells express ICAM-1 and adhere to neutrophil granulocytes, which then act as a linker connecting the tumour cells to the endothelium and thereby enable firm adhesion [90].

It is known that chemokines guide and regulate the migratory activity of cells. Also, it is generally accepted that tumour cells such as leukocytes use chemokines as guidance signals [91, 92]. SDF-1α was the first chemokine reported to play a role in the localization of breast cancer metastases [93]. In addition, it has been shown that fractalkine (CX3CL1), a member of chemokine family, constitutively expressed by prostate carcinoma cells, can guide to the bone marrow endothelium [94, 95].

Moreover, it has been suggested that common neurotransmitter receptor, present on the endothelial surface, provides strong chemotactic signals for tumour cells [96, 97]; and it has been demonstrated that substance P, bombesin, dopamine, and norepinephrine have a stimulatory effect on the migration of breast cancer cells [96].

The second step (adhesion): At this stage, the cells tightly attach to the endothelial cells, using receptors for this interaction that are different from those involved in the rolling process. This firm adhesion to endothelial cells requires activation of a group of endothelial cell adhesion molecules to achieve firm binding with their receptors (integrins) for the successful completion of extravasation [17, 89].

Furthermore, the expression of several integrins, especially of the β_2 subgroup, is restricted to leukocytes, so tumour cells must use different receptors or mechanisms for their adhesion to the endothelium, such as utilizing leukocytes as linker cells [51]. The expression of the α4 integrin has been reported in many different human tumours and tumour cell lines, especially on melanoma and sarcoma [51]. Together with the β1 or β7 integrin, the α4 integrin can act as a ligand for VCAM-1 and fibronectin [98]. In addition, animal models demonstrated that the metastatic capacity of melanoma cells is enhanced through α4β1 integrin interactions with VCAM-1 [98, 99].

Galectins, which are a group of adhesion receptors, are involved in the adhesion step as well, and in several experimental systems galectin-3 expression in cancer cells was associated with a metastatic phenotype [100].

After attachment, the mostly spherical cells spread on the endothelium and actively transmigrate through the endothelial barrier (diapedesis).

The third step of the extravasation process is called diapedesis: Following the strong adhesion, and tumour cell extravasation, the tumour cells do not leave the endothelium intact, but cause irreversible impairment of endothelium integrity after diapedesis [101]. This is understandable because the tumour cells are much larger than leukocytes and it would be difficult to squeeze between endothelial cells without any irreversible damage of this integrity [101].

Adhesion and migration were increased though stimulation by tumour necrosis factor-α (TNF-α) and phorbol-12-myristate-13-acetate (PMA) [102]. Also, chemokine production by cancer cells can also contribute to extravasation [17]. For example, CC-chemokine ligand 2 (CCL2) produced by colon cancer cells and breast cancer cells interacts with CC-chemokine receptor 2 (CCR2) on endothelial cells (ECs) and/or on myeloid cells to increase extravasation and metastasis in the lung [103, 104]. In addition, cancer cell-derived chemokines can attract leukocytes, which facilitate the escape of cancer cells from the immune system and subsequent extravasation success of cancer cells [17].

To cross the vascular endothelium, tumour cells can take two different pathways [102, 103]. They can take either the paracellular route (junctional route), where cells move between neighbouring endothelial cells, which involves localized disruption of endothelial cell junctions [102, 103]. Alternatively, they can use the transcellular route,

where the cells migrate through the endothelial cell body [102, 103].

Although both leucocytes and tumour cells can migrate through the two routes, different subpopulations adhere to specific routes, but the reasons for this are yet to be identified [104].

Two routes have been proposed for this step, the para-cellular route where cells can move between neighbouring endothelial cells itself [104]. To cross the vascular endothelium, leukocytes can take two different pathways. Leukocytes can take either the paracellular route and migrate through interendothelial junctions, squeezing through between adjacent endothelial cells, or leukocytes can take the transcellular route and migrate through an individual endothelial cell body.

The adhesion step imposes structural changes in migrating cells, by changing their shape into round as well as rearranging their cytoskeleton [104, 105]. These changes also occur in the endothelial cells where an evident change of vascular endothelial cadherin has been recorded, as well as increase in vascular permeability [105].

Moreover, adhesion to endothelial cells triggers changes that activate platelet-endothelial cell adhesion molecule (PECAM) and N cadherin, which are demonstrated to play a major role in the diapedesis process [106]. Once migrating cells pass the endothelial layer, they are faced with two obstacles: the basement membrane of the blood vessel and extracellular matrix of the secondary site [107].

Studies have shown that leucocytes utilize MMPs to degrade extracellular matrix to advance to reach the site of the inflammation [108, 109]. It is not clear if the cancer cells apply the same mechanism, which might seem instinctively mandatory [109]. Hence further studies are needed to investigate the role of MMP in cancer cell extravasation.

The adhesion of circulating cancer cells is a critical step in the metastatic process because they interact with many other circulating cells in the bloodstream, including platelets, monocytes, neutrophils and natural killer cells, and these cells modulate the efficiency of cancer cells to extravasate and establish metastatic foci [71].

In addition, the adhesion of circulating tumour cells to the microvasculature endothelium represents a milestone in the extravasation process. The interaction of endothelium with the neoplastic cells determines the physical point of cell exit for successful dissemination and implantation of the tumour in the secondary site [74, 75]. Thus, metastasis should be targeted not only against tumour cells, but also against the host factors that contribute to and support the progressive growth and survival of metastatic cancer cells.

A key point in metastasis is the many pairs of ligand–receptor molecules, including cadherins, integrins, selectins, CD44, and immunoglobulin superfamily receptors, that participate in the metastatic process, and are necessary for the successful dissemination and implantation of the tumour at the secondary site [110].

Cell adhesion is primary determinant of metastasis: Cell adhesion molecules (CAMs) are membrane receptors that mediate cell-cell and cell-matrix interactions, and they are essential for transducing intracellular signals that are responsible for adhesion, migration, invasion, and organ-specific metastasis [70]. Most CAMs such as integrins, E-selectin, and P-selectin, immune-globulin superfamily (IgSF), intercellular cell adhesion molecule-1 (ICAM-1), and vascular endothelial cell adhesion molecule-1 (VCAM-1) have been studied extensively in the process of inflammation [110].

In terms of cancer, on the other hand, studies reveal that tumour cell interactions through selectins and integrins actively contribute to the metastatic spread of tumour cells [70, 111, 112]. Additionally, data show that selectins and integrins significantly link with cancer progression [113, 114]. Furthermore, there is accumulating evidence to indicate the role of selectins and integrins in cancer metastasis in numerous cancer types [70, 112–114]. Also, cancer cell interactions with platelets and leukocytes contribute to cancer cell adhesion, extravasation, and the establishment of a metastatic colony [70].

The adhesion molecules are:

Integrins

They are cell-surface receptors that mediate adhesive interactions between cells and the ECM [70]. The structure of integrins consists of two distinct chains, α- and β-subunits. Eight β- and nineteen α-integrin subunits have been identified in mammals [115]. The integrins bind to the BM and ECM through interaction with a variety of components, such as collagen or laminin, and are involved in both cell-ECM/BM stabilisation interactions and maintenance of the architecture of these structures [41, 70, 80]. In addition, integrins act as a transmembrane mechanical connection between extracellular contacts and the cytoskeleton inside cells [115].

As many human tumours arise from epithelial cells, integrins expressed on epithelial cells generally also exist in tumour cells [41]. Moreover, integrins are expressed on blood cells including leukocytes, T-lymphocytes, monocytes and platelets. They act as receptors for endothelial cell adhesion molecules and mediate blood cell–endothelial cell or blood cell–blood cell adhesion during the inflammatory process [41].

Furthermore, studies have identified a well-established role of integrin during migration and invasion. Integrins regulate cell proliferation, survival and angiogenesis, and all the processes that have been associated with cancer progression [70, 115]. Studies have also demonstrated that integrins are emerging as significant players in metastatic behaviour [70, 80], and variable integrin expression is a common characteristic of cancers, including breast [116], prostate [117], colon [118], and melanoma [119]. Additionally, evidence reveals a correlation between integrin expression levels and pathological outcomes, such as metastasis or survival of the cancer patient [80]. For example, melanomas expressing high levels of $\alpha v\beta3$ have a poor prognosis [120].

Many integrins mediate tumour cell migration and invasion of the BM and ECM surrounding the tumour epithelium, and invasion of the BM of the endothelium of local blood vessels as well [41, 80]. For example, $\alpha v\beta3$ mediates vascular invasion, and its binding to L1 on endothelial cells promotes melanoma cell migration towards blood vessels. Its binding to vitronectin upregulates MMP-2 expression leading to stromal degradation [41, 121]. In addition, both $\alpha v\beta3$ and $\alpha3\beta1$ are involved in cancer cell adhesion to the BM underlying endothelium [121].

Furthermore, Integrins do not just mediate cell-BM adhesion, but ligand binding can also lead to the activation of further intracellular signalling pathways [122], which can consequently stimulate events such as proteolysis or angiogenesis [41]. Additionally, it has been shown that the altered expression of the ECM/BM-associated integrins in carcinomas is involved in cancer metastasis, not only through tumour cell migration into the ECM and surrounding stroma involving integrin-mediated adhesion/de-adhesion events, but also through the release of proteolytic enzymes stimulated by integrin-mediated intracellular signalling events [41].

Selectins

Selectins are vascular receptors that are expressed on activated endothelial cells, and facilitate interactions of tumour cells with platelets, leukocytes, and endothelium [114]. They are three members of the selectin family, leukocyte-selectin (L-selectin), endothelium-selectin (E-selectin) and platelet-selectin (P-selectin). They have been examined as a mediator and potential facilitator of metastasis at sites where arrested tumour cells in the microvasculature have been observed [71, 123].

Further, the physiological functions of selectins are well examined in processes of inflammation, immune response, wound repair, and haemostasis [70]. L-selectin mediates fast rolling of leukocytes on endothelium, while P- and E-selectins support rolling at lower velocities [70]. However, with cancer, selectins mediate by arrest and adhesion of cancer cells, contributing to metastasis. Integrins, however, mediate the interaction between tumour cells and the surrounding environment to further participate in cancer progression [124].

Additionally, it has been demonstrated that expression of the adhesion molecule E-selectin is just up-regulated in response to inflammatory cytokines such as TNF-α and interleukin-1β (IL-1β) [107]. In fact, several studies indicated the importance of pro-inflammatory cytokines for adhesion of tumour cells to the endothelium [41, 107]. For example, increased adhesion rates of pancreatic carcinoma cells to IL-1β and TNF-α at microvascular endothelial cells and mesothelial monolayers respectively have been reported, and associated with a possible increased risk of metastasis [41].

Immunoglobulin superfamily (IgSF)

IgSF is a group of cell surface glycoproteins, comprising the immunoglobulins (IG), T cell receptors (TR) and proteins that have the common feature of having at least one Ig-like domain. IgSF members play a role in the inflammatory process and correlate with the immune system [125]. On the other hand, and due to the widespread expression of immunoglobulin superfamily proteins (IgSF) in cancer cells, they are implicated in cancer progression [126].

There are other cell adhesion molecule (CAM) categories that are known to participate in the adhesion process, including vascular cell adhesion molecule (V-CAM) and ICAM-1, that are related to the immunoglobulin superfamily as well [110]. The involvement of these endothelial molecules is receiving attention, because the expression of V-CAM and I-CAM was significantly higher in the tissue and serum of cancer patients [127, 128].

Secondary tumour foci formation

The final stage of the metastatic cascade is the development of secondary tumour foci at the target organ site [41]. Once tumour cells reach the secondary site,
i) They may be destroyed within 24 h as a result of apoptosis [129].
ii) They might also lie dormant (physical functions suspended or slowed down for a period of time), and possibly be activated at a future time point by, for example, the effects of host immune suppression, or
iii) They may proliferate to form secondary tumours [129].

There are some locations where metastases occur more frequently. For example, the liver, lungs, lymph nodes, brain, bone marrow and adrenal

glands are regarded as common sites of secondary tumours, while the heart and skeletal muscle are rarely affected [130]. Because of the obvious selectivity, this leads to the seed and soil hypothesis that was put forward by Stephen Paget more than 100 years ago. Such a mechanism must exist, to an extent, in the development of secondary tumours [131].

As we have seen, the process of transportation of cancer cells, and transmigration through the blood vessels, is similar to what happens during the inflammatory process [132–136].

Inflammation

Inflammation is the immune response of the body to stimuli or injury, and is characterized by marked vascular changes, including vasodilation, increased vascular permeability, increased blood flow, and increased movement of leukocytes from the blood to the injured tissues, which are induced by the actions of various inflammatory mediators [137, 138].

Extravasation in inflammation

The extravasation of leukocytes is well characterized, and has been reviewed in several aspects. Comparatively little is known about the extravasation of tumour cells, which is part of the haematogenic metastasis formation [51]. Although the steps of the process are basically the same in leukocytes and tumour cells, i.e. rolling, adhesion, and transmigration (diapedesis), the molecules that are involved are different [70]. Another important difference is that leukocyte interaction with the endothelium disrupts the endothelial integrity only temporarily and reversibly, whereas tumour cell interaction leads to irreversible damage of the endothelial architecture; moreover, tumour cells utilize leukocytes for their extravasation as linkers to the endothelium [51].

Leukocyte extravasation is a sequence of events in the journey of leukocytes from the vascular lumen to the interstitial tissue which occurs in a stepwise manner [138–141]. Firstly, individual and rows of leukocytes slowly stumble along the endothelium and adhere to the endothelium. This is called pavementing, and there is a receptor-mediated mechanism [142]. After adhesion, leukocytes insert pseudopods into junctions between the endothelial cells and pass across the basement membrane to escape into extravascular space by the extravasation stage, which is the physical point of inflammatory cells to exit the blood vessels to the inflamed or irritated site [142–144].

Furthermore, leukocytes secrete proteases, such as MMPs, which are a group of proteolytic enzymes whose main function is to degrade ECM protein [145–147]. Matrix metalloproteinases are regarded as key molecules in inflammation, and up-regulated expression of MMP members is often associated with the presence of inflammation [146]. In addition, studies have revealed that inflammatory cells can induce the expression of MMPs, which are crucial for all stages of the inflammatory process, from tissue repair and foreign body elimination to activating cytokines [148, 149].

On the other hand, MMPs have also been implicated in cancer progression and invasion, and are highly expressed in a variety of cancers [150]. In addition, studies have suggested that MMPs induced by inflammatory cells promote angiogenesis, a significant requirement in tumour invasion [151–153]. Thus, there may be common mechanisms associated with inflammation and metastatic tumour development including the chemical mediators that facilitate these processes.

Inflammation and cancer correlation

There is evidence to support the concept that chronic inflammation and continuous irritation participate in cancer development and progression [154–156]. Hanahan and Weinberg identified inflammation as the seventh hallmark of cancer [157].

There is research which indicated that inflammation highlights several aspects of tumour growth, survival and, most significantly, metastasis [157]. In addition, there are data indicating that many molecules, and their activities, are implicated in a link between an inflammatory microenvironment and tumour progression [158, 159]. This might be due to the inflammatory cells and immune-modulatory mediators, such as histamine, serotonin, bradykinin and SP, which may impact on cancer promotion by secreting cytokines, chemokines, proteases and growth factors which induce proliferation and invasiveness of cancer cells [158, 160, 161].

Further, both interleukin-31 (IL-31) and interleukin-33 (IL-33), which are derived from mast cell proteases, are implicated in cancer pathogenesis too [162]. There is evidence to support the concept that the presence of both inflammatory cells and immune-modulatory mediators (IL-31 and IL-33) in the tumour microenvironment is implicated in tumour progression and metastasis. For example, elevated expression of IL-33 has been shown in tumour tissues from colorectal cancer (CRC) patients [162, 163].

Additionally, population-based studies demonstrated that 25% of human cancer cases are related to chronic inflammation, and almost every cancer type is infiltrated with, or surrounded by, inflammatory cells [134]. Thus, the use of anti-inflammatory

drugs, such as steroids and aspirin, may be helpful in the prevention or reduced incidence of several types of cancer. They may also highlight the key role of inflammation in cancer [164–166].

In terms of the potential role that inflammatory mediators play in cancer promotion and progression, there are MMPs and the pro-inflammatory peptide, SP.

Matrix metalloproteinases

Matrix metalloproteinases are a large family of calcium-dependent zinc-containing endopeptidases that are responsible for tissue remodelling and degradation of the ECM. Their substrates include collagens, elastins, gelatin, matrix glycoproteins, and proteoglycan [167]. The 23 expressed MMPs in humans are regulated by hormones, growth factors, and cytokines [167].

The general structure of MMPs shows three domains that are common to almost all MMPs: the pro-peptide, the catalytic domain, and the hemopexin-like C-terminal domain, which is linked to the catalytic domain via a flexible hinge region [168] (Figure 3 A).

These enzymes are expressed as zymogens (inactive), and are subsequently processed by other proteolytic enzymes (such as serine proteases, furin, plasmin, and others) to generate the active forms [169].

Except for membrane-type (MT)-MMPs, all MMPs also share the characteristic of being activated in the extracellular space [170, 171]. The MMPs can also be grouped into eight classes, based on their domain structure. They contain an N-terminal pre-domain that is required for the correct secretion of these enzymes and share structural similarities; however, they differ from each other in their expression profiles and choice of substrate [167].

All MMPs share these characteristics [167]:
• they degrade proteins of the ECM of tissues,
• they contain zinc in the active site,
• they require calcium for their stability, and they function only at a neutral pH.

Additionally, MMPs are excreted by a variety of connective tissue and pro-inflammatory cells (Figure 3 B), including fibroblasts, osteoblasts, endothelial cells, macrophages, neutrophils, and lymphocytes [172].

Further, based on their substrate specificity and structural characteristics, the MMPs are further divided into several subclasses: collagenases (MMP-1, -8, -13), gelatinases (MMP-2, -9), stromelysins (MMP-3, -10, -11), matrilysin (MMP- 7), elastase (MMP-12), and MT-MMPs (MMP-14, -15, -16, -17) [170, 171].

Of the MMPs, a specific subset, namely the gelatinases (MMP-2 and MMP-9), plays a crucial role in a wide variety of physiological and pathological conditions [167, 173, 174]. Amongst them, their potential role in cancer has generated most interest, and has been extensively studied.

Gelatinases (MMP-2 and MMP-9)

Matrix metalloproteinase-2 (MMP-2) and MMP-9 are called gelatinase A and gelatinase B respectively, because gelatine was identified as one of the key substrates for these two enzymes [167]. MMP-2 and MMP-9 are highly similar enzymes in many aspects, but significant differences exist in the regulation of expression, glycosylation, proenzyme activation and substrate selectivity [167]. For example, the 92-kDa MMP-9 contains two N-glycosylated sites in the prodomain and the catalytic domain [175]. MMP-9 expression is observed in normal leukocytes as well as in transformed cells [167]. Also, MMP-9 exists in plasma as a monomer, complexed with neutrophil lipocalin, and as a dimer. In adults, the expression of MMP-9 is restricted to neutrophils [176] and eosinophils [177]. However, MMP-2 is a 72-kDa protein, which is strictly monomeric and, in general, is produced constitutively (produced in a relatively constant amount in all cells) by a wide range of cell types including endothelial cells and macrophages [178].

"Despite their largely overlapping functions, MMP-2 and MMP-9 may even have opposing biological activity as illustrated by the finding that MMP-2 promotes platelet aggregation, but MMP-9 inhibits the same process." [179].

Gelatinase substrates

Gelatinase substrates involve a wide collection of proteins, including ECM proteins, proteinases, proteinase inhibitors, blood clotting factors, chemotactic molecules, both latent growth factors and growth factor binding proteins, cell surface receptors, adhesion molecules and even intracellular substrate [167]. In addition, gelatinases can also break down other ECM proteins such as type IV collagen, elastin, vitronectin, and aggrecan [180]. However, currently, the relevance of these events *in vivo* is unclear, but the cleavage sequences of both MMP-2 and MMP-9 have been mapped with the substrate phage [181, 182].

The substrate specificities of MMP-2 and MMP-9 are similar but not identical and the minor differences in catalytic domain have functional consequences in the gelatinases' substrate selectivity [167].

It has been found that in the human brain, neurons produce MMP-9 in regions where collagen is not present [183]. As a result, the ability of the enzyme to degrade bioactive peptides was
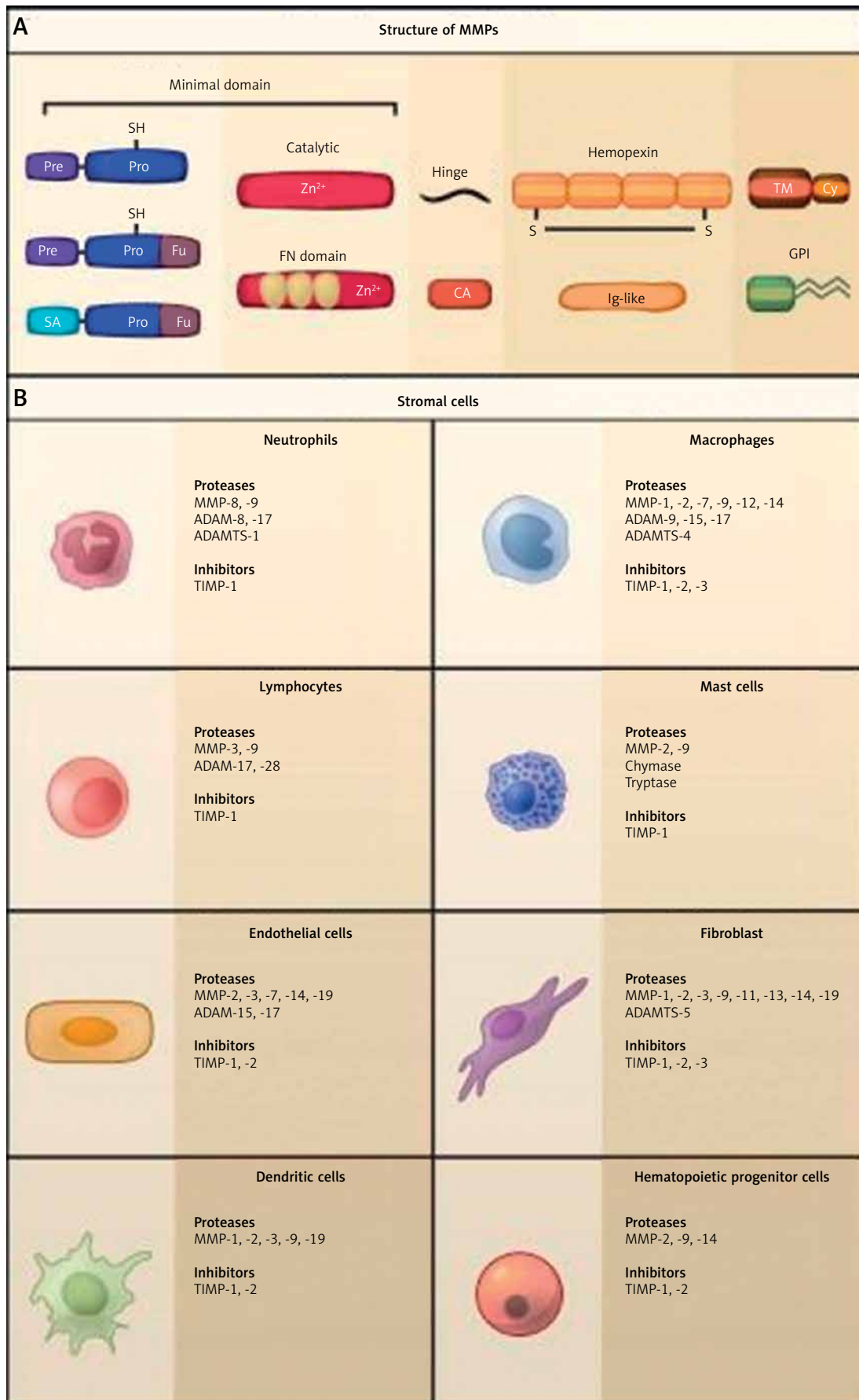
Figure 3. MMP composition and expression in the stroma [168]

examined, particularly with respect to the tachykinin peptides (SP, neurokinin A, neurokinin B, and kassinin) [183]. Additionally, at the same time, It has been shown that the active form of MMP-9 degraded SP at a 30-fold greater rate than the previously reported value for a representative collagen-derived peptide [183].

Proenzyme activation

As I mentioned before, the gelatinases are secreted as inactive pro-forms, and they need to be activated externally for full catalytic activity. Activation occurs by disruption of a Zn^{2+}-cysteine bond, either by removing the prodomain or by modifying the cysteine residue in the prodomain [184]. The activation of the gelatinases takes place on the cell surface or in the extracellular milieu [185, 186]. Further, a number of proteases can activate gelatinases *in vitro* (dissolution) and *in vivo* (bioavailability), suggesting that there is a significant crosstalk between different protease systems [167].

Regulation of gelatinase

To avoid and prevent unwanted tissue damage, it is very important to carefully control the protease activity. For this reason, protease activity is typically regulated at many levels, including transcription, secretion, activation, and by the action of proteinase inhibitors (TIMPs), which are either natural or synthetic gelatinase inhibitors [167].

Natural TIMP proteins are significant endogenous regulators of MMP activity in tissues, and act by forming tightly bound inhibitory complexes with MMPs [187]. Additionally, natural TIMP proteins are produced by a variety of cell types, and are induced or constitutively expressed by most tissues and body fluids [188]. Furthermore, TIMP-1 works as a natural inhibitor of MMP-9 (146), whilst TIMP-2 is an inhibitor of MMP-2 [189]. Thus, a balance between MMP and TIMP activities is involved in both normal and pathological events such as wound healing, tissue remodelling, angiogenesis, invasion, tumorigenesis and metastasis [167].

Physiological and pathological roles of gelatinases

It has been shown that gelatinases play a role in a wide variety of physiological [173] and pathological conditions [174]. During the natural reproduction process, the cells of the implanting embryo secrete gelatinases and other MMPs which are required for this natural invasive process. Matrix degradation and remodelling occur during reproduction, growth and development [173]. In addition, the gelatinases participate in wound healing (physiological process) [190], and are typically expressed from the beginning to the end of the healing process [191].

On the other hand, when gelatinases are present at too high a level, for too long, or in the wrong places, and their activity becomes uncontrolled, they begin to degrade proteins that are not their normal substrates [192]. This can result in off-target destruction of proteins, such as growth factors, receptors and ECM proteins, that are essential for normal physiological activity, and so they eventually lead to pathological conditions [192, 193].

Increased gelatinase activity has been observed in a variety of pathological conditions including cancer, inflammatory disorders, infective diseases, degenerative diseases of the brain and vascular diseases [193, 194]. Thus, the old paradigm that gelatinase's role is restricted to matrix digestion might not be the case. There is new evidence suggesting that both MMP-2 and MMP-9, collectively, are important in the pathogenesis of inflammatory, infectious, and neoplastic diseases in many organs [167, 195].

Gelatinases and inflammation

Several studies have indicated that MMPs, including gelatinases, represent a marker of inflammation because they regulate several functions related to inflammation, including bioavailability and activity of inflammatory cytokines and chemokines [196]. Although MMP-9 is expressed by neutrophils and inflammatory stimuli, MMP-9 expression can be stimulated by other cells including endothelial cells, alveolar cells, macrophages, fibroblasts, and other connective tissue cells [197].

Additionally, leukocytes have large amounts of protease-containing granules, which are rapidly excreted and delivered to the extracellular space after leukocyte activation [198]. One of these granule types, called gelatinase granules, also contains integrins, which are one of key players in the regulation of leukocyte migration in inflammation [198, 199].

Although the extracellular matrix is a key substrate for the gelatinases, these enzymes also can degrade other substrates such as cytokines and chemokines, thereby resulting in different physiological and pathological processes [200]. In other words, chemokine and cytokine cleavage by gelatinases can have varying impacts on their biological properties, ranging from potentiation and inactivation, to antagonist formation [200].

Recent studies suggest that both MMP-2 and MMP-9 have certain chemokines and cytokines as their substrates, which act as mediators and regulators of inflammation. Also, both MMP-2 and MMP-9 have a wide range of pro- and anti-inflammatory effects on leukocytes, endothelial cells and other cell types [201].

Moreover, cytokines, including IL-1, TNF-α, and transforming growth factor α (TGF-α), are likely to regulate genes of MMP expression that regulate the migratory activity of inflammatory cells [184]. Additionally, MMP-9 can cleave the inactive membrane-bound forms of TNF-α and transforming growth factor-β (TGF-β) to generate their corresponding active forms, which in turn mediate the expression of adhesion molecules and promote the migration of cells [191, 202].

Similarly, both gelatinases can generate the active form of IL-1β from its inactive pro-form [203]. Further, signals that upregulate and activate MMP expression can also include the production of pro-inflammatory cytokines (such as TNF-α, IL-1, IL-4 and IL-6), and integrin binding is also a significant step for leukocyte migration [204].

The MMP is highly expressed in any disease or condition that is associated with inflammation, and proteolysis is considered a hallmark of the inflammatory process [205]. In addition, several MMP inhibitors are used as anti-inflammatory drugs in periodontal and vascular diseases, acting through limiting MMP production or activation [206, 207]. Thus, anti-inflammatory therapy is still the mainstay and the requirement in the control of both the inflammatory process and inflammatory mediators [206].

Tetracycline: Interestingly, studies have demonstrated that tetracyclines, in addition to their anti-microbial activity, inhibit inflammatory cell migration to sites of inflammation and also act as MMP inhibitors. The ability of tetracycline to inhibit MMPs is independent of their anti-microbial activity [208]. Tetracycline act on two levels: they suppress gelatinase expression [209], and directly inhibit gelatinase activity through a zinc chelating (removing) effect [208]. Thus, tetracycline derivatives have entered clinical trials as MMP inhibitors [210].

The first evidence that MMPs, including gelatinase, might contribute to cancer development and progression derives from the field of inflammation. The role of chronic inflammation in carcinogenesis was examined via several epidemiological studies looking at pro-inflammatory mediators, along with other factors involved in the inflammatory response [157, 211].

For this reason, anti-inflammatory therapy is still a mainstay in the treatment of equine joint disease (Goodrich and Nixon 2006). Nonsteroidal anti-inflammatory drugs (NSAIDs) are a common first line treatment in joint disorders that require alleviation of pain and control of inflammation.

Gelatinases and cancer

Cancer studies have found that MMPs, including gelatinases, can regulate multiple cellular functions including cell growth, apoptosis, angiogenesis, invasion, and metastasis by cleaving growth factor precursors, cell adhesion molecules and other bioactive proteins, and critical molecules in these processes [153, 172, 212].

Furthermore, studies have demonstrated that many malignant cells produce both MMP-2 and MMP-9 [213, 214]. Both MMP-2 and MMP-9 have certain chemokines and cytokines as their substrates, that act as mediators and regulators of metastatic processes; in addition, they have a wide range of pro- and anti-inflammatory effects on leukocytes, tumour cells, endothelial cells and other cell types [201]. As tumours consist of cancer cells and stroma, cancer cells may be the source of gelatinases in some cases, but in most cases, only stromal cells express gelatinases [215].

The chronic inflammation associated with some cancers can further stimulate cancer progression due to the release of MMPs from the inflammatory cells too [167, 215]. Expression of MMP-2 and MMP-9 has been observed in cancers of the breast, colon, lung, skin, ovary and prostate [172]. Also, with increased gelatinase expression in these cancers types, there is an increase in invasiveness and metastasis in addition to a decrease in overall survival of cancer patients [172].

Indeed, increased gelatinase expression may be dependent on the stage of the cancer. For example, in melanoma, increased expression of MMP-9 is found in the early stage of cancer, but the opposite is true at a late stage [216]. Meanwhile, in breast and colon cancer, MMP-9 expression has been correlated with the survival and formation of distant metastases [217–220]. Further, MMP-9 has been regarded as a prognostic marker and as a target for therapeutic intervention in cancer [221].

Additionally, there are several interactions between tumour cells and the tumour microenvironment, which involve ECM, growth factors and cytokines associated with ECM, as well as surrounding cells (endothelial cells, fibroblasts, macrophages, mast cells, neutrophils, pericytes and adipocytes) [222, 223].

Also, it has been found that cancer cells typically migrate in response to migratory signals and this cellular response can be either non-directional movement (chemokinesis) or directed migration along a chemical concentration gradient of the signal inducer (chemotaxis) [167].

Gelatinases and cell adhesion, migration, and epithelial to mesenchymal transition: The movement of cells is highly related to the MMPs' proteolytic activity, a disintegrin and metalloproteinase (ADAMs), regulating the dynamic ECM–cell and cell–cell interactions during migration [153, 172].

The main functions of gelatinase in cell migration and invasion are degradation of ECM molecules, such as collagen type IV and laminin-5 (an extracellular matrix substrate for cell adhesion and migration); disruption of cell-matrix adhesion; disruption of cell-cell interaction; and exposure of cryptic migration promoting sites. In addition, there is cleavage of matrix-associated latent factors [224] (Figure 4).

A recent study reported that hyaluronan (hyaluronic acid), which is widely distributed throughout connective tissue, promotes cancer cell migration by increasing matrix metalloproteinase secretion, and specifically increased levels of the active form of MMP-2, through Rho kinase-mediated signalling [225].

Moreover, several integrins play an active role in regulation of cell migration because they can serve as substrates for MMPs [226]. It has been suggested that integrin α3β1-mediated interaction with laminin-5 stimulates adhesion, migration and invasion of malignant glioma cells [227]. Hence, inhibition of the association of gelatinases with cell-surface integrin appears to offer a highly specific means to target these enzymes without inhibiting their catalytic activity in multiple cell types including endothelial cells, tumour cells and leukocytes [152, 167].

Furthermore, the signals that upregulate the expression and activation of MMPs involve the production of pro-inflammatory cytokines and integrin binding [204]. Therefore, it is plausible that inhibition of MMP activity through control of its proteolytic activity at the cell surface can greatly reduce the migration and invasion of cells by blocking the production of pro-inflammatory cytokines [228].

Morozevich et al. have demonstrated for the first time that α5β1 integrin promotes and controls invasion of breast carcinoma cells by regulation of MMP-2 collagenase expression. This can occur either through signalling pathways or by direct recruitment of MMP-2 to the cell surface [229]. In addition, Morozevich et al. have reported that inhibition of the invasiveness of these cells in vitro, associated with down-regulation of α5β1 integrin, occurs through inhibition of the expression and secretion of MMP-2 [229].

Thus, it is evident that there are complex interactions between MMPs and a variety of other inflammatory factors. As such, some of their roles in inflammation and cancer are still hypothetical [167]. Because the role of MMPs, including gelatinase, in extravasation are poorly understood, further studies need to be performed to see if gelatinase is regulated by the same factors that control the adhesion process.

Key points:
- Gelatinases have certain chemokines and cytokines as their substrates which act as mediators and regulators of inflammation and metastatic processes.
- Chronic inflammation associated with some cancers can further stimulate cancer progression due to the release of MMPs.
- Gelatinases have the ability to regulate multiple cellular functions including cell growth, apoptosis, angiogenesis, invasion, and metastasis by cleaving growth factor precursors and cell adhesion molecules.
- Gelatinases have a wide range of pro- and anti-inflammatory effects on leukocytes, tumour cells, and endothelial cells.

Several integrins play an active role in regulation of cell migration because they can serve as substrates for MMPs.

Substance P

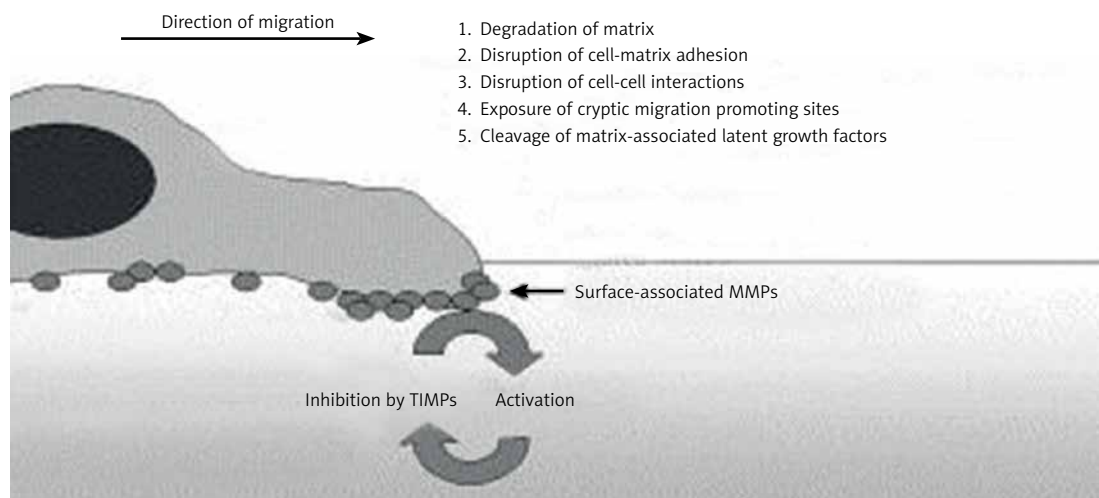Substance P is a neuropeptide from the tachykinin family, which is widely distributed in both the

Direction of migration

1. Degradation of matrix
2. Disruption of cell-matrix adhesion
3. Disruption of cell-cell interactions
4. Exposure of cryptic migration promoting sites
5. Cleavage of matrix-associated latent growth factors

Surface-associated MMPs

Inhibition by TIMPs   Activation

Figure 4. Functions of MMPs in cell migration and invasion [167]

central and peripheral nervous systems. A variety of biological functions in the central nervous system, including emotional behaviour, pain perception, stress, depression, anxiety, emesis, migraine, and alcohol addiction are linked to the release of SP [195, 230].

In the peripheral nervous system and other tissues, SP acts as a local hormone (tachykinin), and causes hypotension and vasodilatation and may cause contraction of smooth muscles [231, 232]. In addition, it is thought to be involved in the regulation of respiratory mechanisms, regulation of the cardiovascular system, sensory perception, in neuronal survival and degeneration, sensory perception, movement control, gastric motility, salivation and micturition [233, 234].

Substance P is also involved in multiple processes including inflammation and metastatic dissemination after binding to the tachykinin NK-1 (NK1) receptors [235].

Substance P and inflammation

Over the past two decades, SP has been identified as a significant mediator in the development and progression of inflammation [236–238]. It acts as a vasoactive mediator, increasing vascular permeability and mediating the function of inflammatory cells. These impacts, collectively termed neurogenic inflammation, comprise microvascular plasma leakage, neutrophil recruitment, and inflammatory mediator synthesis, as well as increasing the vascular permeability and mediating the function of inflammatory cells [234, 239–241].

In addition, there are data indicating that SP participates in inflammation by interacting with the NK-1 receptor expressed in nerves (excitatory neurons and secretory cells) and inflammatory cells, such as macrophages, mast cells and T cells. The activation of these cells results in the release of cytokines and chemokines as active factors, as well as other neuropeptides that modulate inflammation [195, 236]. Also, there is increasing evidence that SP modulates the activities of several different leukocytes that characterize both acute and chronic inflammatory responses [239, 242, 243].

Furthermore, there is a large body of evidence demonstrating that SP possesses a variety of potent effects, including the production of cytokines, such as TNF-α, IL-1, IL-4 and IL-6 [244, 245]; SP selectively activates TNF-α synthesis in mast cells too [246].

Moreover, SP stimulates the release of TNF-α, which mediates the expression of such adhesion molecules as E-selectin, ICAM-1 and VCAM-1 on vascular endothelial cells, thereby leading to leukocyte migration [241, 247, 248]. Additionally, SP may play a role in the pathogenesis of such diverse diseases as arthritis, asthma, and inflammatory bowel disease [249].

Substance P and cancer

Numerous studies have reported the involvement of the substance P (SP)/neurokinin (NK)-1 receptor complex in cancer [161, 250, 251]. In addition, it has been demonstrated by many studies that SP acts via NK-1R as a mitogen on several human cancer cell lines such as glioma, neuroblastoma, retinoblastoma, laryngeal carcinoma, and melanoma [161, 252, 253]. Further, its presence in the tumour microenvironment strongly suggests a role for the SP/NK-1R complex in tumour development and progression [254, 255].

Also, NK-1R, a receptor of SP, is overexpressed not only in several normal cells [254, 256], but also in neoplastic cell types [252, 254, 257]. It is also known that malignant tissues express more NK-1 receptors compared to benign tissues. Additionally, the tumour cells that express most malignant phenotypes show increased NK-1 receptor expression [161].

There are studies that demonstrate that substance P, acting via the NK1 receptor, probably plays a role in several biological functions related to cancer including angiogenesis, invasion and metastasis [161].

Moreover, substance P has been implicated as a mediator in cancer cell extravasation through the blood-brain barrier (BBB) to form cerebral metastasis [258].

Also, it has been reported that SP is involved in pancreatic cancer perineural invasion, and that SP induces cancer cell proliferation and invasion, as well as the expression of MMP-2 in pancreatic cancer cells [161].

Activation of the neurokinin-1 receptor (NK-1R) by substance P initiates several intracellular signalling pathways, including the nuclear factor-κB (NF-κB) pathway, culminating in the release of pro-inflammatory cytokines such as IL-1β and TNF [235, 259]. IL-1β and TNF, in turn, upregulate expression of the adhesion molecules involved in extravasation [260]; blocking the NK-1 receptor has been shown to reduce expression of TNF [260].

Furthermore, the combination of SP and insulin-like growth factor-1 (IGF-1) significantly increased the number of cells attached to the fibronectin matrix, and increased the expression of integrin α5 [261].

Previous work in this laboratory (M. Elhousiny, unpublished data) has shown that SP can increase the expression of integrin molecules in cancer cells, accompanied by an increase in adhesion to endothelial cells. Additionally, and because integrins play an active role in regulation of cell migration, they can serve as substrates for MMPs, which

might upregulate and activate MMPs. Blocking the NK-1 receptor reduced the expression of the integrin, and inhibited adhesion of the cells that upregulate MMP expression. Also, inhibition of the NK-1 receptor may potentially block the release and activity of MMPs, and subsequently might slow metastasis.

Hence, there is a need for more research to explore and identify the role of MMPs in cancer promotion and progression. In particular, examining the role of substance P in cell adhesion and migration could mean that neurokinin-1 receptor antagonists could represent a novel and promising approach and access for treating patients with cancer.

Key points:
- SP acts as a vasoactive mediator, increasing vascular permeability and mediating the function of inflammatory cells.
- SP produces cytokines, such as TNF-α, IL-1, IL-4 and IL-6.
- A receptor of SP is overexpressed in several normal and neoplastic cell types.
- SP stimulates the release of TNF-α, which mediates the expression of such adhesion molecules as E-selectin, ICAM-1 and VCAM-1 on vascular endothelial cells, thereby leading to leukocyte migration.

SP via the NK-1 receptor can increase expression of integrin molecules in cancer cells.

Conclusions

Cancer is probably the most devastating and heterogeneous disease and is a major cause of mortality in Australia. Metastasis is the process used by cancer cells to spread throughout the body and is associated with an increase in mortality for several cancers. Inflammation has been closely linked with cancer. The process of translocation of cancer cells and transmigration through the blood vessels is similar to what is seen with immune cells during the inflammatory process, and it is possible that inhibiting inflammation can reduce cancer progression. Matrix metalloproteinases are the main proteases that have been associated with inflammatory processes as well as cancer cell metastasis and are involved in degradation of the extracellular matrix. Substance P is a neuropeptide involved in multiple processes including inflammation and metastatic dissemination. In addition, SP via the NK-1 receptor can increase expression of integrin molecules in cancer cells, and that might upregulate and activate MMPs. Blocking the action of SP via the NK-1 receptor may block the activity of MMPs and consequently slow metastasis. Thus, the development of antagonist molecules of the NK-1 receptor represents an important opportunity for exploiting these molecules as novel therapeutic agents.

Conflict of interest

The authors declare no conflict of interest.

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