# Chapter 10
# Cancer: Nurture and Nature

**Romano Demicheli**

**Abstract** The currently prevalent somatic mutation theory of carcinogenesis and metastases explicitly assumes that cancer is a cellular disease, i.e. a disease of the control of cell proliferation and/or cell differentiation. Accordingly, explanations should always be sought for at a gene and/or gene product level, regardless of the level of organization at which the phenomenon is observed. Such a reductionist approach characterized the century-old effort to find cancer cell singularities, absent in normal cells, without apparent success, however. More recently alternative views have been put forward, assuming that cancer is a tissue based disease involving disturbed interactions within the tissue architecture.

In this review, selected reports on normal tissue homeostasis and bone marrow contribution to both tumour cells and tumour stroma are reviewed. Regarding normal tissues, the existence of a complex homeostatic system actually involving the whole organism emerges. Regarding tumours, remarkable similarities with normal tissue activities are apparent, providing some evidence that tumours share many biological features and processes with normal tissues. The review supports the concept that cancer is a tissue based disease and that its pathological nature may result from unbalanced/untimely activation of otherwise normal physiological processes.

**Keywords** Tumour homeostasis • Tumour stroma and cells • Bone marrow • Pre-metastatic niche • Wound healing • Similarities between tumour and normal tissue

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## 10.1 Introduction: Homeostasis Traits from Tissue Damage Repair

The early perception of cancer was substantially borrowed from the paradigms of bacterial infections [1–2]. Indeed, cancer was regarded as pathologic phenomenon occurring at cellular level, a genome-driven disease, where the accumulation of a sufficient number of alterations in key genes results in "cell transformation". Transformed cells were viewed as *aliens* intruding a vulnerable idle microenvironment. Cell transformation was believed to be an irreversible process: "Once a cancer cell, always a cancer cell".

Yet, this paradigm was progressively challenged by a number of experimental and clinical findings, highlighting the crucial role of tumour stroma in carcinogenesis, tumour development and clinical behaviour and providing evidence that normal cells may display cancer-like behaviour while, conversely, cancer cells may regain normal cell traits [3–8]. The novel cancer image, where tumours look like pseudo-organ structures more than invading hordes, supported reasonable explanations for clinical findings and suggested new concepts such as tumour dormancy and accelerated metastasis growth due to primary tumour removal [9–10]. It also advocated the occurrence of some kind of homeostatic effect of primary tumour upon distant metastases, apparently mimicking the organ homeostasis that succeeds the growth process. In this review, similarities between normal tissue and tumour behaviours will be examined by a parallel scrutiny of normal homeostatic mechanisms and tumour relationships with the host organism. This survey further supports the concept that tumours share many biological processes with normal tissues, although these "normal" processes are often de-contextualized and result in pathological outcome.

Seminal knowledge on tissue homeostasis emerged from investigations on damage repair, where dramatic reawakening of the tissue building machinery is required. Both parallel processes between wound healing and morphogenesis [11] and the role of growth factors and cytokines [12] have been recognized, as well as the role of bone marrow (BM), which provides inflammatory mature cells to injured tissues. Furthermore, a number of recent reports, in both animals and humans, indicate that bone marrow also supplies cells capable of producing non-hematopoietic tissue. Since the nature of such cells as well as their denomination remain debated, they will be henceforth referred to as bone marrow-derived cells (BMDCs).

### *10.1.1 Animals*

In animals, the contribution of BMDCs to epithelial and stromal cells at steady state conditions is detectable in several organs (skin, lung, liver, gastrointestinal trait), although at different frequencies, with maximum levels into the skin [13–15]. Accordingly, a few cells within the BM, a rare population that can be estimated to

represent about 0.001–0.01% of the BM nucleated cells [16], can originate in vivo non-hematopoietic tissue, a phenomenon that is enhanced in tissue damage repair.

Skin wound healing has been extensively investigated [14, 15, 17–21]. Locally, BMDCs increase early, peak after a week and then decrease to a stable level estimated to be 10–20% [15]. Most of them are spindle-shaped dermal fibroblast-like cells [15, 17, 19, 21] that produce type III collagen, not synthesized by skin-resident dermal fibroblasts [15]. A lower fraction originates epithelial cells [13, 14, 18–20], which are detectable in epidermis, hair follicles, and sebaceous glands. Skin damage activates the release of chemokines from the injured site, which interact with BMDC receptors (e.g. CCL21/CCR7) and induce mobilization and local recruitment [17, 20, 22]. A study focused on the role of BMDCs in the local angiogenesis process concluded that they play a major role by paracrine mechanisms without endothelial differentiation [22].

A positive correlation between tissue damage and BMDC homing with contribution to stromal and epithelial cells was ascertained in other organs, including lung and salivary glands [23–26].

### *10.1.2 Humans*

In humans, the conversion of BMDCs into epithelial cells was observed in patients receiving BM or other organ transplantations from gender discordant donors.

In archival specimens, hepatocytes and cholangiocytes from BMDCs ranged from 4 to 43% [27], suggesting that hepatocytes and cholangiocytes derived from circulating BMDCs, which were able to replenish large numbers of hepatic parenchymal cells. In lung transplantations, recipient-derived epithelial cells were detected in bronchial epithelium of the transplanted organ [28]. A markedly higher degree of chimerism was observed in epithelial structures displaying signs of chronic injury, such as squamous metaplasia (24% *versus* 9.5%). Another report [29] confirmed chimerism in up to 6.6% of epithelial cells in bronchial and alveolar tissue, providing evidence that extrapulmonary precursor cells, putatively BMDCs [30], are able to contribute to pulmonary regeneration.

After BM transplantation, BMDCs were identified as differentiated cells in each of the parenchymal components of salivary glands: acini, ducts and stroma (0.65–1.44%) [31]. Higher frequency of microchimerism (~10%) was found in the buccal mucosa of a few patients, suggesting higher BMDC contribution for tissues with higher turnover. A positive association between the proliferative activity and the BMDC epithelial commitment was observed in colonic mucosa as well [32], where BMD epithelial cells frequency was significantly higher in samples indicating non-specific colitis.

A remarkable investigation on the effect of skin injury as inducer of cell mobilization from other body compartments in 44 patients with total body surface burn area of 30–60% and, for comparison, in 23 healthy subjects has been recently published [33]. Cells expressing stem cell-associated markers, such as CD133, CD34,

and CXCR4 as well as small cells expressing profile markers of pluripotent cells (Oct-4$^+$ Nanog$^+$ SSEA-4$^+$ CXCR4$^+$ lin$^-$ CD45$^-$) were detected. Changing serum concentrations of Stroma Derived Factor 1 (SDF-1), Hepatocyte Growth Factor (HGF) and Vascular Endothelial Growth Factor (VEGF) were measured. The mobilization of putative stem cells increased significantly 5 days after skin injury, which may reflect the serum dynamics of chemoactive factors and the time needed to the cell pool amplification.

In conclusion, wound healing, far from being a local process, is basically a systemic process involving complex homeostatic mechanisms that only recently are beginning to be understood.

## 10.2 Tumours: Wounds That Do Not Heal

### *10.2.1 Tumour Cells from Bone Marrow*

It is well known that a few tumours have haematological origin (e.g. leukaemia). Yet, even non-haematological tumour cells may derive from BM cells. For instance, in recipients of sex mismatched BM, peripheral blood stem cell or organ transplantation, developing a successive solid cancer, BMDCs were found to contribute to tumour cells. In particular, in a few patients with oral squamous cell carcinoma, most, if not all, tumour cells were donor-derived [34–36], indicating that tumours were apparently generated by the transplanted BM cells. The contribution of BM to tumour cells was also detected, although less extensively (1–5%), in other tumours (lung adenocarcinoma, larynx squamous cell carcinoma, glioblastoma, Kaposi sarcoma, mucoepidermoid carcinoma of the parotid gland, breast cancer, papillary thyroid carcinoma and Barrett's adenocarcinoma) [37–40].

A seminal investigation on the possible contribution of BMDCs to tumour cells was performed in murine gastric cancer development from *Helicobacter* infection [41]. After infection, rapid increase of inflammatory BMDCs within gastric tissue was observed, but there was no early engraftment and differentiation as epithelial cells. Engraftment was first seen later and, in chronically infected mice, a large population of BMDCs within the gastric mucosa expressed intestinal-type mucins and displayed phenotype of the metaplastic lineage. Epithelial dysplasia increased in severity over time and eventually resulted in carcinoma. All of the intraepithelial neoplasia cells arose from BM cells.

Somewhat different behaviour was observed for intestinal adenomas in female mice. BM derived columnar-like epithelial cells were detected in the adenomas of all small bowel and colon specimens at a rate of 0.02%. When animals were injected with murine lung cancer the contribution of BMDCs to lung tumours was nearly 1%. In a parallel analysis of human histological specimens of colonic adenoma, skin cancer and squamous cell carcinoma of the lung, none of the skin cancer cells showed BMDC origin, 1–4% of the adenoma epithelial cells and 20% of the lung

cancer cells were from BMDCs. Authors propose that BM participates to neoplasia at the level of *developmental mimicry*, whereby BMDCs are called into a neoplastic environment where they respond to developmental cues and adopt phenotypes similar to the surrounding neoplastic epithelial cells [42].

In summary, BMDCs may develop as a constituent of tumour cell populations, generating, in some cases, the entire tumour mass, the same as they may accomplish in wound healing.

### *10.2.2 Tumour Stroma from Bone Marrow*

Inflammatory cells infiltrating tumour bulk, once assumed to act to attenuate tumour development, were successively found to play roles in promoting progression of many types of cancer [43].

A number of reports evaluated the dynamics of BMDC homing and differentiation in tumour stroma. In a human pancreatic cancer cell line transplanted in mice [44], BMDCs appeared early as inflammatory cells accounting for 13% of myofibroblasts and 25% of endothelial cells at 2 weeks. Later, percentages evolved to 40% and 26% respectively, suggesting that BMDCs contribution dynamics is different for endothelial cells and myofibroblasts. Differently, BMDC contribution to tumour endothelial cells appeared substantially lower (about 0.4% or less) in another study on spontaneous adenocarcinoma of the mouse prostate [45]. Detailed analysis of cell position revealed that while BMDCs were discernible in perivascular position in both primary tumour and lung metastases none were at the luminal surface. BM was suggested to be a reservoir for cells that increase tumour angiogenesis via endocrine/paracrine mechanisms, while the tumour endothelium would be derived primarily from the local environment. BMDC contribution to angiogenesis was also comparatively analysed in ischemic retinas, Lewis lung carcinoma (LLC) and B16 melanoma [46]. The spectrum of BM involvement was dependent on model system with SDF-1α as a key permissive trigger. In ischemic retinas, BMDCs provided long-term neovascularization and BMDCs expressing CXCR4 and CD133 participated directly in blood vessel formation. In tumours, LLC had BM-derived neo-vessels (17%) and exhibited both increased SDF-1α serum levels and site-specific expression; whereas B16 melanoma did not show either site-specific SDF-1α expression or BM derived neo-vessels. B16 melanomas still contained little to no BM contribution when growing in an environment of elevated serum SDF-1α level, whereas blood vessels had a density similar to that of LLC tumours, suggesting that tumour neovascularization occurs through redundant mechanisms, possibly tumour type related.

BMDCs contribute considerably to carcinoma-associated fibroblasts (CAFs), which express α-smooth muscle actin (myofibroblasts). In mouse models of inflammation-induced gastric cancer, at least 20% of CAFs originated from BM and their recruitment was blocked by CXCR4 inhibition, while myofibroblasts expansion was reduced by TGF-β inhibition [47]. CAFs are likely to be a special phenotype

that BMDCs adopt after recruitment in neoplasias. Indeed, in chronic pancreatitis by caerulein and in carcinogenesis by DMBA [48], cancer-associated, but not pancreatitis-associated BMD stellate cells expressed the cancer related specific marker CELSR3, suggesting that BMDCs can adopt different phenotypes, conceivably responding to the different environmental signals.

Integrin α4β1 promoting the homing of BMDCs to neo-vasculature, tumour derived transforming growth factor β1 (TGF-β1) attracting BMSCs, and BMSC derived IL-17B attracting tumour cells, were suggested as mediators of tumour-stroma interactions [49, 50]. In another remarkable investigation, a human breast cancer cell line yielding vigorously growing tumour xenografts (labelled as "instigator") was implanted in one flank of nude mice, while another indolent cell line (labelled as "responder") was implanted into the contralateral flank [51]. Instigating tumours, even when small (0.08% of total body mass), facilitated the outgrowth of already-established, otherwise-indolent tumour cells located contralaterally. Release of soluble factors (e.g. osteopontin) enabled instigating tumours to communicate and perturb BM, the functional activation of which conveyed activated BMDCs to the stroma of responding tumours, fostering growth. This effect involved also micrometastases and, interestingly, a xenografted human tumour surgical specimen from colon cancer.

The notion that operative injury may worsen the prognosis of cancer patients was supported by a study on the effect of surgery (gastrotomy) on the course of LLC in mice [52]. Twelve days after operation, the tumour volume almost doubled in mice after gastrotomy with significant increase of BMDCs, microvessel density and proliferating cells, while the number of apoptotic cells was significantly reduced in comparison with controls. Interfering with the SDF-1/CXCR4 signalling pathway inhibited the recruitment of BMDCs and negated completely the acceleration in tumour growth after operation. The mobilization of BMDCs, however, could be different after different operative injuries, as this phenomenon was undetectable after hepatectomy.

In summary, BMDCs may play in tumours and in wound healing similar supportive roles in the form of stroma cells that regulate the local "parenchymal" cell population by reacting to microenvironmental signals.

### *10.2.3 The Pre-metastatic Niche*

More recently it was discovered that, before the arrival of tumour cells, adjustments occur in metastatic sites that make them conducive for successive metastasis development. This process results in a metastatic niche providing support to metastasis-initiating cells, by analogy with the physiological niches that support stem cells in healthy tissues. The local tissue tuning before tumour cell arrival has been labelled *pre-metastatic niche* and this cellular 'bookmarking' was first reported for lung metastases from LLC and B16 melanoma in mice [53]. Before tumour implantation, minimal BMDCs were observable in the lungs. By day 14 after

tumour implantation, but before the arrival of tumour cells, a remarkable cluster formation of BMDCs was detectable near terminal bronchioles and distal alveoli. On day 16, established BMDC clusters dictated the contours of future metastatic lesions. Individual tumour cells, associated with pre-existing BMDC clusters, were visible by day 18 and progressed to micrometastases by day 23. Intradermal injection of LLC cells resulted in BMDC cluster formation limited to the lung and liver with no clusters in other organs. In contrast, B16 melanoma tumour cells induced the formation of BMDC clusters in multiple tissues such as lung, liver, testis, spleen and kidney. Remarkably, pre-treatment with melanoma derived conditioned medium resulted in redirection of LLC metastasis to sites frequently observed in B16-melanoma. Implanted LLC tumour cells were associated with increased fibronectin expression at the lung pre-metastatic niche, compared with the baseline level. The fully formed pre-metastatic niche ($VEGFR1^+$ BMDCs, fibroblasts and fibronectin) highly expressed SDF-1, creating a chemokine gradient attracting tumour cells that thereby developed a complete metastatic lesion.

Pre-metastatic changes preceding tumour seeding were observed in a mouse model of spontaneous lymph node metastasis, where sentinel lymph nodes were significantly enlarged before detectable metastasis, and were enriched in functional blood vessels, an effect absent in the next lymph nodal station, implying a selective mechanism [54]. Contrasting with cancerous related lymphadenopathy, the morphology of vessels in endotoxin induced lymphadenopathy was unchanged, suggesting nodal reaction by different modalities. In humans, the process of vascularisation in the metastatic versus non-metastatic versus non-cancerous inflamed axillary lymph nodes was consistent with findings in the animal model [54]. Of note, in patients with prostatic cancer, HSCs and cancer cells occupy just the same endosteal niche and compete with each other for niche occupancy on the osteoblast [55].

Factors involved in the pre-metastatic niche development and in the following cancer cell homing and survival include hypoxia-inducible factor-1 [56] and coagulation, which is required for the recruitment to distant sites of monocytes/macrophages [57]. Focal vascular hyper-permeability involvement, with endothelial cell-focal adhesion kinase activity facilitating cancer cell homing to lungs, has been also observed [58]. A few reports point out the prominence of extracellular matrix components, such as tenascin [59] and periostin [60]. In particular, the role of periostin emerges from an elegant and detailed investigation on a mouse breast cancer model with spontaneous lung metastases [60]. Authors provide evidence that (i) the metastatic process is sustained by a subpopulation of tumour initiating cells (TICs), accounting for 3% of all tumour cells in both primary tumour and lung metastases, which are the only cancer cells able to benefit from periostin; (ii) the metastasis efficiency is determined by the stromal periostin production that is upregulated in response to the TGF-β released from cancer cells; (iii) periostin, in a feed-back interaction with Wnt ligands of TICs, boosts Wnt signalling activity that promote cell survival and metastatic colonization. VCAM-1 expression in breast cancer cells was also reported to provide survival advantage to cancer cells [61]. Taken together, these reports indicate that interactions of cancer cells with

extracellular matrix components of the metastatic niche, activating pro-survival tumour cell processes, like Wnt, Notch and PI3K pathways, are necessary in order to support the metastatic phase.

## 10.3 Components of the Homeostatic Process

BM is a source of cells directly supporting the homeostasis of tissues (in steady state conditions and after lesions) and able to originate cells from the three distinct germ-cell layers (ectoderm, mesoderm, and endoderm). Moreover they play a key role in tumour development. Trans-differentiation, cell fusion processes and non-hematopoietic primitive stem cells (SCs) in BM were hypothesized to explain such phenomena. Trans-differentiation and fusion have been questioned as main processes [62, 63], while several populations of non-hematopoietic SCs potentially able to differentiate into given cells in tissues have been described in the BM. In particular, a population of very small embryonic-like stem cells (VSELs) was identified, which are apparently a good candidate for a leading role in tissue homeostasis. VSELs have been firstly purified from murine BM and from several other adult murine organs (e.g., brain, liver, skeletal muscles, heart, and kidney) [64]. A corresponding population of small (4–7 μm) $CD133^{+}$ $Lin^{-}$ $CD45^{-}$ cells that display embryonic-like morphology have been identified in human umbilical cord blood, in mobilized peripheral blood and in adult BM [65]. Human VSELs expressed Oct4 and Nanog in their nuclei and displayed the SSEA-4 antigen. The number of circulating VSELs increased during tissue or organ injuries (e.g., heart infarct, stroke, or acute colitis), as well as after administration of certain drugs mobilizing HSCs into peripheral blood (e.g., G-CSF) [66]. BM-derived VSELs displayed the ability to differentiate in vivo into multiple mesenchymal lineages and generate osseous tissues. When injected into the hearts of mice that had undergone ischemia/reperfusion injury, VSELs induced improved global and regional left ventricular systolic function and attenuated myocyte hypertrophy in surviving tissue [67].

Whatsoever such cellular performers may be, it is crucial to understand how they participate to the collective action by communicating with other participants in this process. Usually it was believed that soluble factors such as cytokines, chemokines, growth factors and bioactive lipids released from a given cell type and circulating through the whole organism are able to induce responses by other cells endowed with specific receptors. Recent research, however, is elucidating a much more complex and efficient communication system, the core of which is a busy trafficking of microvesicles.

Microvesicles (MVs), frequently observed by electron microscopy in the interstitial space of tissues and for long time considered cellular debris, have been recently recognized as functionally relevant [68]. MVs are spherical membrane fragments containing a cargo of cytosol including a distinct and definite combination of lipids, proteins and nucleic acids (mRNA, miRNA and DNA), i.e. a non-random sample of the molecular repertoire of the originating cell [69]. MV surfaces express the adhesion

molecules of the cell of origin, allowing specific capture by target cells that recognize them, which may be modified by surface interaction [70]. Most important, MVs may induce epigenetic changes in target cells by transferring selected arrays of mRNA and miRNA associated with ribonucleoproteins. Transferred mRNA can be translated after entering the target cells [69]. For example, human endothelial progenitor cell-derived MVs may activate an angiogenic program in recipient quiescent endothelial cells [71]. MVs not only mediate tissue-specific changes in mRNA by direct delivery of mRNA but also by induction of mRNA from the target cell [72]. Remarkably, some miRNAs are selectively accumulated within MVs released by adult human mesenchymal SCs and absent in the cells after MV release, whereas others are retained within the cells and not secreted in MVs [73]. This suggests a regulated process of miRNA compartmentalization and secretion by MVs.

MVs may have a functional role for tumours. Exposing normal recipient cells to bioactive MVs constitutively shed by certain human cancer cells caused the recipient cells to acquire a transformed phenotype [74]. At pre-metastatic niche level, melanoma-released MVs induced expression of a network of interconnected extracellular matrix factors responsible for tumour cell recruitment, trapping and growth [75]. Tumour-initiating cells from a human renal cell carcinoma released MVs shuttling specific mRNAs and miRNAs that triggered angiogenesis and promoted the formation of a pre-metastatic niche in the lung [76]. Human lung cancer cells changed the genetic phenotype of human BM cells by inducing lung-specific mRNA by exposure to pelleted microvesicles [77]. Of interest, BM cells co-cultured with lung melanoma and sarcoma, expressed lung-specific genes, raising interesting possibilities of bidirectional cross talk between cancers and the normal host tissue. These findings once again suggest that cell structures are less stable than previously considered and that cell phenotype, including cancer phenotype, might be exportable.

## 10.4 Concluding Remarks

The above reported findings indicate that BM routinely provides a contribution of specific parenchymal cells to various tissues especially after tissue damage. Remarkably, the homing of BMDCs into the damaged tissue is associated, to some extent, with the emergence of gene expression patterns corresponding to phenotypes of stroma and parenchymal cells of the “invaded” tissue (e.g. myofibroblasts and keratinocytes in the skin) (Fig. 10.1). This phenotypic change apparently relies on dominant effects of the tissue microenvironment upon imported cells. This concept is strongly supported by a few focused investigations [78, 79].

Tissue homeostasis in a given organ is apparently a complex and very integrated system actually involving the whole organism. Indeed, progenitor cells with different commitment (e.g., HSCs, MSCs and ESCs) in addition to pluripotent cells (e.g., VSELS) may reside in virtually all organs, among which BM is a main reservoir. When homeostasis alterations occur, signalling pathways (e.g. SDF-1/CXCR4) may

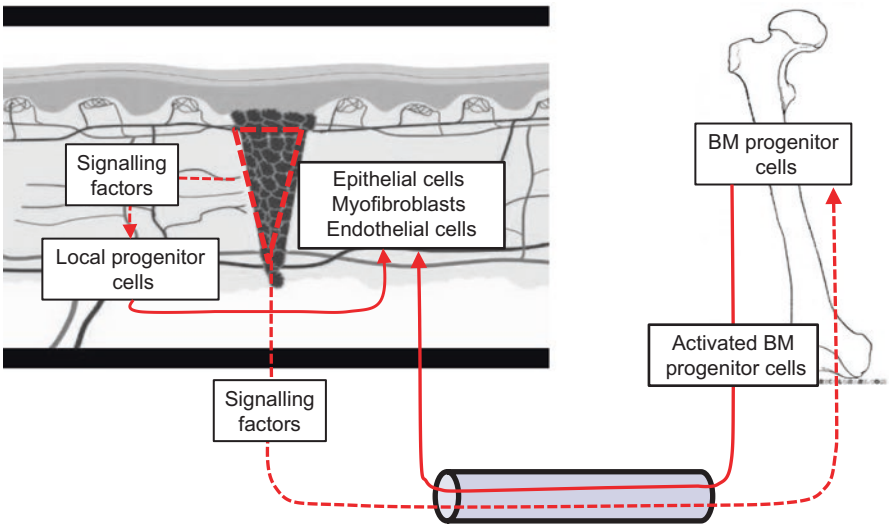


**Fig. 10.1** Outline of tissue damage repair. Tissue lesion induces release of signaling factors locally activating progenitor cells and, via blood circulation, reaching bone marrow where they activate and mobilize further progenitor cells quickly homing in the damaged area. Activated progenitor cells originate repair stroma cells (myofibroblasts and endothelial cells) and also epithelial cells, although at different percentages. Bone marrow derived inflammatory cells are also recruited in the wound (not reported in the schematic figure). The coordinated interaction of all cells results in the progressive tissue repair and the following long lasting tissue remodeling

activate and, if needed, mobilize them. Activated SCs secrete a variety of growth factors, cytokines, chemokines and bioactive lipids that regulate their biology and orchestrate interactions with the surrounding microenvironment. In addition to soluble factors, activated SCs also secrete MVs, conveying packaged signalling factors, including genetic information, which may change the phenotype of the target cells, locally or at distance. Thus, one can conceive that, while cellular populations may be relatively stable, transcriptional regulation, a key determinant of the phenotype of a particular cell, may shift between different cell types [80]. What remains stable and, if damaged, induces cellular conversions to re-achieve the original condition is apparently the whole tissue architecture.

In this "normal" landscape, some "hallmarks of cancer" actually appear as familiar traits of normal cell populations. Angiogenesis is a current feature in tissues during physiological conditions and damage repair. The process we label as invasion is usually adopted by non-neoplastic cells that, mobilized from distant organs, enter target tissues. Tumour cell activities, underlying the metastatic process, basically appear as expression of the current cell trafficking network, with which they share molecular mechanisms (e.g. the SDF-1/CXCR4 axis). The tumour ability of creating the "tumour microenvironment" (Fig. 10.2) apparently parallels the ability of tissues of maintaining the "normal microenvironment" or creating the "repair microenvironment" (Fig. 10.1). Moreover, the metastatic development does not

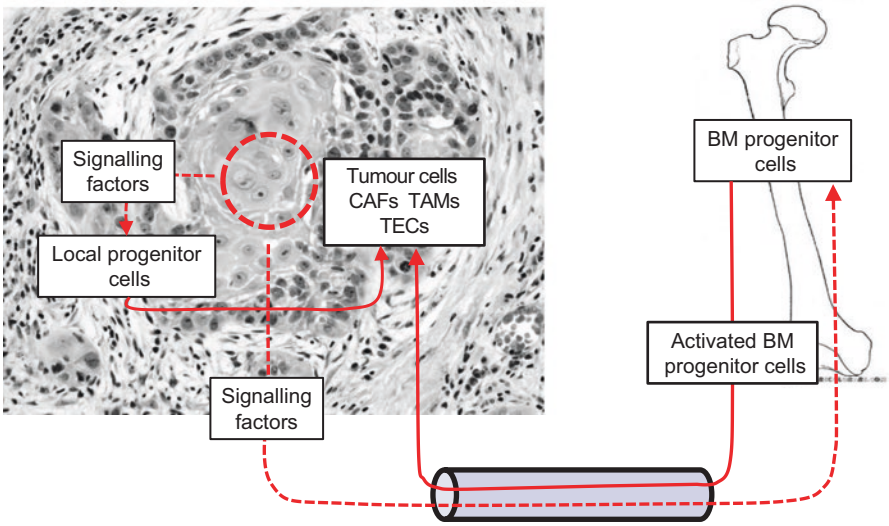


**Fig. 10.2** Outline of tumour actions underlying growth. Tumour presence induces release of signalling factors that activate local progenitor cells and, via blood circulation, reach bone marrow where they mobilize and activate further progenitor cells quickly homing in the tumour area. Activated progenitor cells originate tumour stroma cells (CAFs and endothelial cells) and also tumour cells, although at different percentages, while this ability is still undecided for local progenitor cells. Bone marrow derived inflammatory cells are also recruited in the wound (not reported in the schematic figure). The coordinated interaction of all cells results in the tumour further growth

apparently diverge from such a general processing structure and is probably firmly related to inter-tissue connections (Fig. 10.3).

The recently proposed tumour hierarchical structure, including tumour stem/progenitor cells and differential metastatic capacity, further supports the parallelism between tumour and tissue structures, including the presence of stem/progenitor cells at local level and the ability of recruiting stem/progenitor cells from other sites. Furthermore, tumour cell niches are comparable to normal cell niches and are sometimes identical to them, so that both tumour and normal stem cells compete for the same site. Local conducive changes allow for recruitment and homing of stem/progenitor cells in both cases. Tumours, therefore, appear well integrated in the complex physiologic homeostatic network and it is difficult to refute the notion that tumours, far from being harsh invaders hijacking "normal" performances, share most traits with normal cells, although the normal (or normal-like) processes they use are often de-contextualized and result in pathological processes.

Most important, the central tumour hallmark, the *genome instability,* implies a paradigm of normality where lineage pathways are unidirectional and narrowly restricted, because of irreversible inactivation of genes that are required for alternate pathway selection. We are now discovering that not only normal cells could, at certain conditions, jump between lineages, but there are also specific ways to

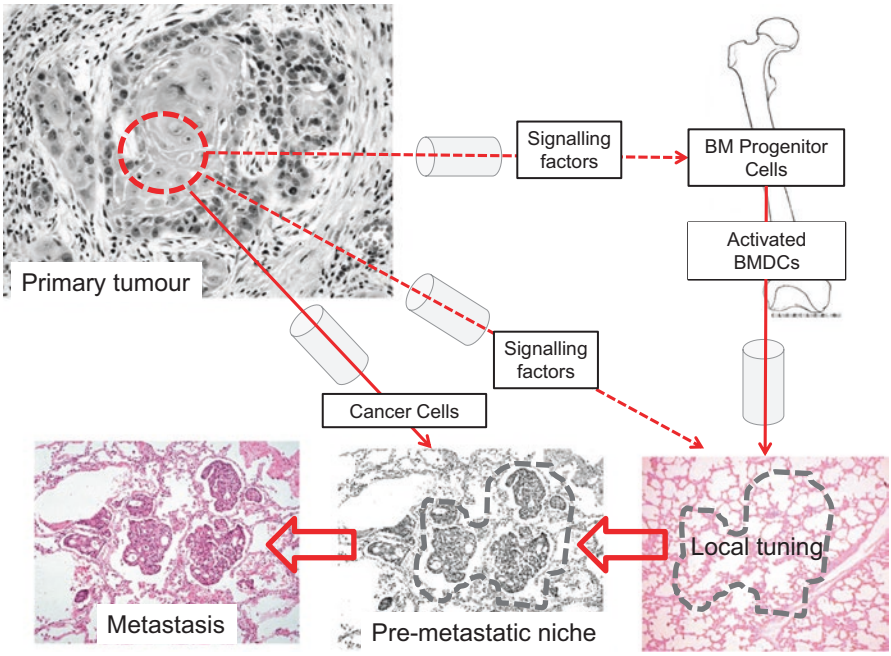


**Fig. 10.3** Outline of the metastasis development via the pre-metastatic niche. Primary tumour signals (soluble factors, MVs) act in a manner that before the arrival of tumour cells, adjustments occur in metastatic sites that make them conducive for successive metastasis development. Bone marrow is involved and BMDCs are activated, mobilized and undergo a selective homing process resulting in metastatic site tuning that makes it conducive for tumour cells. This process results in a metastatic niche providing support to metastasis-initiating cells, by analogy with the physiological niches that support stem cells in healthy tissues. The local tissue tuning before tumour cell arrival has been labelled *pre-metastatic niche.* The further steps of the metastatic foci, such as dormancy or growth, are depending on several local and systemic factors

transfer genetic information between cells resulting in phenotypic change. Tumours, therefore, seem to lose the exclusivity for most of their typical traits and the notion could not be ruled out that their pathological nature results from unbalanced or untimely activation of otherwise normal physiological processes.

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