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Mesenchymal Stem Cells: Miraculous Healers or Dormant Killers?

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Abstract
Mesenchymal Stem Cells (MSCs) are a heterogeneous population of fibroblast-like cells which maintain self-renewability and pluripotency to differentiate into mesodermal cell lineages. The use of MSCs in clinical settings began with high enthusiasm and the number of MSC-based clinical trials has been rising ever since. However; the very unique characteristics of MSCs that made them suitable to for therapeutic use, might give rise to unwanted outcomes, including tumor formation and progression. In this paper, we present a model of carcinogenesis initiated by MSCs, which chains together the tissue organization field theory, the stem cell theory, and the inflammation-cancer chain. We believe that some tissue resident stem cells could be leaked cells from bone marrow MSC pool to various injured tissue, which consequently transform and integrate in the host tissue. If the injury persists or chronic inflammation develops, as a consequence of recurring exposure to growth factors, cytokines, etc. the newly formed tissue from MSCs, which still has conserved their mesenchymal and stemness features, go through rapid population expansion, and nullify their tumor suppressor genes, and hence give rise to neoplastic cell (carcinomas, sarcomas, and carcino-sarcomas). Considering the probability of this hypothesis being true, the clinical and therapeutic use of MSCs should be with caution, and the recipients' long term follow-up seems to be insightful.

Keywords Mesenchymal stem cell · Carcinogenesis · Cancer stem cell · Epithelial mesenchymal transition · Mesenchymal epithelial transition

Introduction

Stem cells are clonogenic cells that have two distinctive features: multipotency and self-renewal capacity [1]. The surge of studies on stem cells emerged by the discovery of a subset of bone marrow residing haematopoietic stem cells (HSCs) which give rise to all blood cell types [2]. Later on, studies by Friedenstein and colleagues reported that the bone marrow stroma can generate mesodermal cell lineages following heterotopic transplantation in mice; an observation suggestive of the presence of non-haematopoietic multipotent precursor cells within the bone marrow [3]. These precursors were a subset of fibroblast-like cells that could be easily isolated by their ability to adhere plastic surfaces *and were shown to have hallmarks of stemness* [4]. As a result, the term "Mesenchymal Stem Cell (MSC)" was assigned and accepted to refer to these newly identified precursor cells [5].

Bone marrow has been considered the main source of MSCs (bmMSCs), for many years. However; these stem cells are present in many other adult and fetal tissues (with few exceptions) [6]. In an attempt to standardize the definition of an "MSC", the International Society for Cellular Therapy (ISCT) proposed the concept of essential minimal criteria for MSCs in culture [7]. The four minimal defining criteria for MSCs are: 1) adherence to plastic under standard tissue culture conditions, 2) expression of CD105, CD73, CD90, 3) lack of expression of CD45, CD34, CD14/CD11b, CD79/CD19 and HLA-DR surface markers, and 4) differentiation into adipocytes, osteoblasts and chondroblasts in vitro [7, 8].

MSCs: From Bench to Bedside

It didn't take long for MSCs to become a subject of clinical research as potential therapeutic modalities in medicine, mostly because of their immunoregulatory and tissue regenerative properties [9], as well as simplicity of isolation and expansion [10]. The use of MSCs in clinical settings began with high

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enthusiasm and the number of MSC-based clinical trials has been rising since 2004 (Fig. 1a), and till now, there has been over 750 registered clinical trials in different phases aimed at evaluating the potential of MSC-based cell therapy worldwide (Fig. 1b). A number of these trials have shown efficacy of these cells in the treatment of conditions like: GvHD, Crohn's disease, rheumatoid arthritis, ischemic stroke, myocardial infarction, chronic heart failure, type 1/2 diabetes mellitus, spinal cord injury, bone fractures/defects, chondral/osteochondral defects, cirrhosis, amyotrophic lateral sclerosis, and cerebral palsy [11].

However, it is important to note that not all MSC-based clinical trials have met their primary endpoint of efficacy and claims of benefit may be biased by strong commercial interests [12]. The very unique characteristics of MSCs that made them suitable cells to be used in clinical trials, might give rise to complications and unwanted outcomes, including tumor initiation, progression and metastasis.

Until 2007, most published data were in favor of anti-tumor properties of MSCs [13, 14], but a turning point was encountered when Karnoub and colleagues showed that co-injection of humans MSCs with breast cancer cell lines accelerated tumor growth, and metastasis [15]. Their observations led to further studies scrutinizing anti-tumor vs. tumor promoting properties of these cells [16]. From studies published thus far, it is assumable that MSCs might be among the important players in favor of tumor growth and progression.

MSCs' Role in Cancer Progression

Tumor microenvironment can be considered as a swamp hosting many anti-tumor and tumor promoting factors such as MSCs. The active migration of endogenous and exogenous MSCs to tumor sites has been demonstrated in several models [17–19]. Upon arrival to tumor microenvironment, MSCs exhibit tumor promoting characteristics, due to direct and indirect signals they receive in the new milieu. These cells has been shown to increase proliferation, mobility, dormancy [20] and resistance to therapy [21] in neoplastic cells, by transdifferntiation to cancer associated fibroblasts (CAFs) [21–24], promotion of angiogenesis and lymphangiogenesis [25–28], stimulation of epithelial-to-mesenchymal transition (EMT) [29–32], suppressing tumor immune responses [21], induction of stemness in cancer cells [33–38] and probably acting as tumor initiating cells [39, 40].

Bearing these in mind, the question of whether the clinical application of MSCs would help cancer development/progression will be raised. There are studies demonstrating that this assumption could be right. For instance, several murine and human studies have shown the donor origin of CAFs in tumors of transplant recipients. In 2008, for the first time, Mishra et al. showed that human bone marrow–derived MSCs become activated and resemble CAFs on prolonged exposure to conditioned medium from MDA-MB231 human breast cancer cells [24]. Further studies by Spaeth [41] and Quante [18] provided additional evidence for transdifferentiation of donor MSCs to CAFs in recipients' tumors. Interestingly, in 2009, Worthley and colleagues reported Y-chromosome positive CAFs in female patients with gastric cancer and rectal adenoma, with a history of bone marrow transplants from male donors [42].

Tumor promoting functions of transplanted MSCs via angiogenesis has been attributed to their ability to secrete angiogenic factors such as VEGF and TGF-beta [27, 28, 43], transdifferentiation to pericytes [44, 45]/endothelial cells [46], and recruiting endothelial progenitors [47]. Moreover, studies have shown that MSCs increase mobility, migration and consequently metastasis capacity of neoplastic cells [36, 48–51]. These observations have been linked to the ability of MSCs to induce EMT in neoplastic cells [30, 31, 35]. Furthermore their role in tumor progression by suppressing immune responses has been shown by several studies (submitted review). In the subsequent sections of this paper, we will review and discuss the possible roles of MSCs in induction of stemness in cancer cells, and their role as tumor initiating cells.

MSCs' Induction of Stemness in Cancer Cells

Cancer stem cells (CSCs) are rare immortal subpopulation of cells within tumors that can both self-renew and give rise to

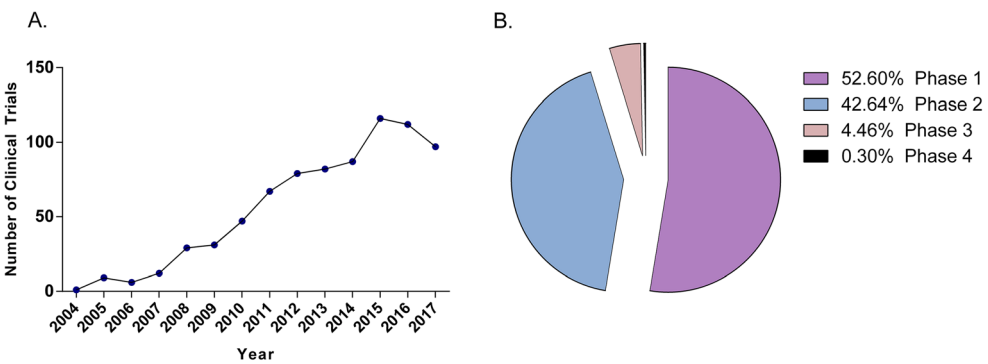

Fig. 1 **a** Number of registered clinical trials of MSC-based therapy. **b** Clinical phases of MSC-based therapy. (https://clinicaltrials.gov/)

diverse cell types in tumor milieu [52, 53]. Presumably, tumors' resistance to therapy and recurrence can be attributed to the quiescent nature of these cells [54]. MSCs supply an advantageous tumor microenvironment for the maintenance of CSCs by secreting a variety of cytokines and formation of tumor cell hybrids by entosis or fusion [52, 53, 55–57].

Cabarcas and colleagues demonstrated that MSCs can promote cancer stemness through NF-κB pathway and secretion of CXCL12, IL6, and IL8 [58]. Moreover, it has been shown that MSCs promote undifferentiated state in neoplastic cells by producing BMP antagonist, Gremlin-1 [59], BMP2,4 [60], IL-6 [38, 61], CXCL1, CXCL7, CXCL8 [62], CCL5 [63], CXCR2 ligands (CXCL1, 5, 6, 7, 8) [64], activation of the JAK2-STAT3 pathway [65], FOXD1-ALDH1A3 Signaling [66] and through repression of FoxP2 expression [67]. Induction of stemness in cancer cells by MSCs has been shown in ovarian [60, 68], breast [64, 67], gastric [69], colon [62], and brain neoplasms [70].

Interestingly, El-Badawy and colleagues demonstrated that indirect co-culture of cancer cells and MSCs causes MSCs to acquire some properties of CSCs upon exposure to cancer cell-secreted factors and displayed properties of cells with enhanced sphere formation capacity [34]. This observation raises the question that whether MSCs used for therapeutic purposes can give rise to tumor initiating cells.

MSCs as Tumor Initiating Cells

In 2008, Berger and colleagues reported an osteosarcoma of donor origin in a patient who had received allogenic bone marrow transplant for β-thalassemia, 17 years earlier [71]. The isolated neoplastic cells expressed MSC markers at very high levels [71] and hence, one can assume that MSCs transplanted along with hematopetic stem cells had given rise to the osteosarcoma in the recipient. A more direct observation of engrafted MSCs transition to tumor initiating cells was published by Qian et al. [72]. They reported a sarcoma of donor origin (K3 cell line), found on the tail of a female rat after injection with male rat bone bmMSCs [72]. Considering these observations in addition to the capacity of MSC transdifferntiation to different cell lineages, it is presumable that engrafted MSCs may give rise to a variety of neoplasms in the recipient.

Spontaneous Tumoral Transformation of MSCs

Several studies have demonstrated that Mouse MSCs (mMSCs) are predisposed to acquisition of transformation events after long-term in vitro culture favoring clonal selection of transformed cells [73]. These observations prompt the concern that in the human settings, the *ex-vivo* expansion of human MSCs (hMSCs) before clinical application may also cause spontaneous neoplastic transformation after long-term culture.

MSCs as the Cell of Origin for Sarcomas

Sarcomas are heterogeneous mesenchymal malignancies arising from the bone, cartilage, muscle, peripheral nerves, adipose and fibrous connective tissues [74]. The definite cells of origin for sarcoma subtypes remain unclear [74]; however, there is increasing evidence suggesting that they probably arise from mesenchymal pluripotent stem cells [39, 74].

For instance, a growing body of evidence indicates an MSC origin for Ewing's sarcoma. About 85% of Ewing's sarcomas harbor translocations resulting in the fusion of the *EWS* gene with *FLI1* gene [75]. Ectopic *EWS-FLI1* expression in mMSCs results in transformation of these cells to Ewing sarcoma-like cells in vivo [76, 77]. Furthermore, the knockdown of *EWS-FLI1* expression in Ewing's Sarcoma results in conversion of the tumor cells to MSCs [78]. By the same token, both spontaneous and induced MSC models for osteosarcoma have been shown [79–82] and in both osteosarcoma cells and transformed MSCs, aberrations in genes encoding P53 pathway components have been identified; and targeted mutation in *p53* of mMSCs causes development of osteosarcoma [81, 83].

Boeuf and colleagues have reported that less differentiated chondrosarcomas have more similarity with MSCs, while more differentiated ones were more similar to chondrocytes [84]. This observation suggests that chondrosarcoma formation could be the result of deregulated MSC differentiation to chondrocyte. In case of synovial sarcomas, which are often characterized by the presence of *SS18-SSX1*, *SS18-SSX2* or *SS18-SSX4* chimerical genes [85], it has been shown that silencing of the fusion gene expression in neoplastic cells induces the expression of mesenchymal markers [86]. Additionally, the expression of *SYT-SSX1* in hMSCs induces a transcriptional profile very similar to the Synovial sarcoma cells [87].

In mouse models of Liposarcoma, the expression of *FUS-CHOP* in both bone marrow and adipose-derived mMSCs gave rise to Liposarcoma like tumors [88, 89]. Furthermore; some subtypes of Rhabdomyosarcomas are formed by the expression of either *PAX3-FKHR* or *PAX7-FKHR* fusion genes in MSCs, pushing MSC differentiation towards a myogenic lineage while inhibiting terminal differentiation [90].

All these observations suggest that multipotent and long-lived MSCs may act as the tumor initiating cells for some sarcomas upon the expression of specific fusion genes and it is presumable that engrafted MSCs may give rise to a variety of sarcomas in the recipient. On the other hand, and taking into

account the cell fate conversions, these engrafted MSCs may give rise to carcinomas and Carcinosarcomas of donor origin in the recipient as well. In general, the changes from one cell type to another are observed during embryonic development, tumor formation/progression and somatic cell reprogramming [91]. In vitro and in vivo studies have shown that MSCs have the capacity to differentiate into all three embryo cell lineages (ectoderm, mesoderm and endoderm) in special media [92].

MSCs as the Cell of Origin for Carcinoma-Sarcomas

Carcinosarcomas (also known as sarcomatoid carcinomas) are biphasic neoplasms composed of malignant epithelial and mesenchymal elements. They can arise in diverse organs, such as the respiratory system [93–95], guts [96–99], gall bladder [100], pancreas [101], spleen [102], peritoneum [103], skin [104, 105], ovary [106], fallopian tubes [107], uterine [108], urinary system [109, 110] and adrenals [111].

Several hypotheses have been proposed on the basis of carcinosarcomas' pathology seen in different organs (Fig. 2) [112]. Convergence theory (multiclonal theory) suggests that two independent tumors with separate epithelial and mesenchymal origin have collided (Fig. 2a) [113]. Divergence theory (monoclonal theory) argues that both carcinomatous and sarcomatous components are derived from a single pluripotent stem cell that subsequently diverges along separate epithelial and mesenchymal pathways (Fig. 2b) [114]. Finally; conversion theory proposes that the sarcomatous element of the tumor represents a metaplastic transformation from the epithelial part (EMT) (Fig. 2c) [115]. The reverse mechanism is also supposable and MSCs could be the cells of origin to sarcomatous component and late in tumorigenesis, sarcomatous subclones go through partial MET and result in carcinomatous component formation (Fig. 2DA.

Monoclonality of Carcinosarcomas is supported by multiple levels of evidence such as: the co-expression of cytokeratins and epithelial membrane antigens in both carcinomatous and sarcomatous components [116], concordance of *TP53* and *K-ras* mutations [117], identical patterns of X chromosome inactivation [118], and similar losses of heterozygosity [119].

MSCs as the Cells of Origin for Carcinomas

The epithelial barrier is exposed to several exogenous insults and the homeostasis of this tissue should be precisely balanced according to cell loss and production. One of the possible cell sources of this homeostasis is considered to be local and bone marrow leaked MSCs [120]. Following an epithelial injury, the MSCs are recruited to this site using the same mechanisms as immune cells [121]. Upon their arrival, MSCs regulate the repair process by differentiation into several kinds of stromal and damaged cell types [122, 123] including myofibroblasts

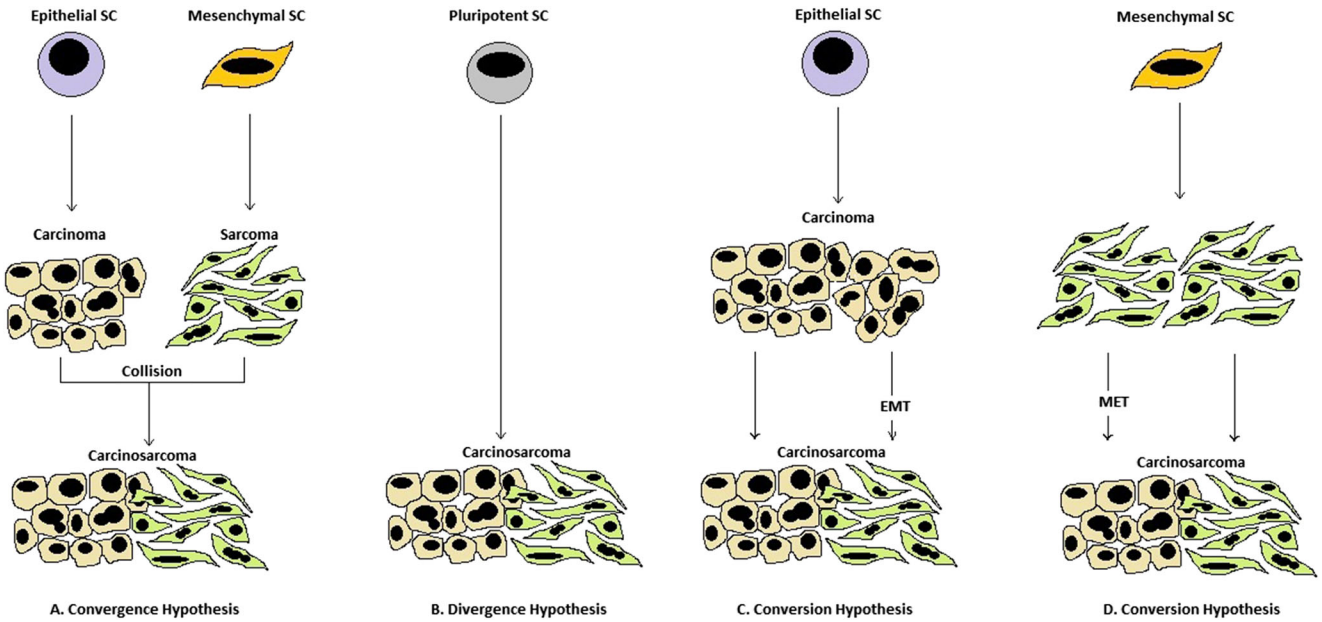

Fig. 2 Theories proposed to explain Carcinosarcoma cell of origin; (A) Convergence theory or multiclonal theory suggests that two independent tumors with separate epithelial and mesenchymal origin have collided; (B) Divergence theory or monoclonal theory argues that both carcinomatous and sarcomatous components are derived from a single pluripotent stem cell; (C, D). Conversion theory proposes that a single epithelial or mesenchymal stem cell gives rise to carcinoma or sarcoma, respectively. Subsequently theses neoplasias go through metaplastic transformation and give rise to carcinosarcoma; SC:Stem Cell; EMT: Epithelial to Mesenchymal Transition; MET: Mesenchymal to Epithelial Transition

[124], endothelial cell [125], and epithelial cells of the injured tissue.

The presence of MSC derived epithelium in injured ectodermal and endodermal tissues has been demonstrated by several lines of evidence. An interesting observation in regard to hMSC transdifferentiation to keratinocytes was reported by Sivamani and colleagues [126]. They reported that contact co-culture of hMSCs and keratinocytes, caused the hMSCs to adopt epithelial morphology and express keratinocyte markers [126]. Using specific differentiation protocols, several *in-vitro* models confirmed that acquisition of keratinocyte phenotype is a pretty probable event in epithelial regeneration after injury [127–131]. Interestingly, corneal keratinocyte can also be generated using MSCs [132, 133].

Transdifferentiation of MSCs to alveolar pneumocytes and their role in repair of respiratory epithelium has been studied widely. These cells are well recognized for their ability to differentiate into type II alveolar pneumocytes in damaged lungs, which is critical for re-epithelization in acute lung injury [134, 135].

In gastrointestinal tract, the epithelium needs to be renewed rapidly, in order to conserve its function. Tissue damage, for instance following local irradiation, enhances engraftment of bmMSCs in the epithelial linings of the gut, revealing a close relationship with the course of tissue regeneration [136]. Ferrand and colleagues demonstrated that MSCs fusion with gastrointestinal epithelial cells could be the predominant mechanism by which they acquire epithelial characteristics when in close contact with gastrointestinal epithelium [137]. Furthermore, MSCs transdifferentiation to hepatocytes following liver injury has been reported [138–141] and endocrine cells of pancreas (beta cells) can also be regenerated using MSCs [142–144].

MSCs' role in repair of urothelial tissue has been demonstrated as well. Ning and colleagues reported that co-culture of hMSCs with urothelial cells, led to development of urothelial features in MSCs [145]. Tian et al. further revealed that MSCs can differentiate into urothelium when cultured in conditioned medium derived from bladder cell culture [146].

Bearing these in mind, it is supposable that in physiologic states, at least some parts of regenerated epithelium are originated from MSCs and the broader (the area) and longer (time duration) the injury, the more MSCs going through transdifferentiation (MET, Mesenchymal to Mesenchymal Transition (MMT), Mesenchymal to endothelial transition (M-endT)).

In 2013, the stem cell misplacement theory (SCMT) was proposed by Wang et al. to explain carcinoma formation and some obscure aspects of this event [147]. They proposed that invasive cancers are the result of misplaced epithelial stem cells which come to the wrong land of connective tissue by accident and give rise to carcinoma in the stroma *de novo* [147]. Herein we describe an alternative model for carcinoma formation, arising from misplaced MSCs in epithelial tissue, going through defective MET (Fig. 3).

The primary insult causes disruptions in the epithelium and its basement membrane (for example UV, radiation, etc., Fig. 3a). This injury attracts immune cells along with bmMSCs by means of cytokines/chemokines and adhesion molecules (Fig. 3b,c) [121]. bmMSCs pass through the injured basement membrane, enter the epithelial milieu and transdifferntiate to epithelial tissue (MET), mostly due to direct contact with epithelial cells and encountering their growth media (Fig. 3d,e,f) [126, 145, 146]. At the very beginning these misplaced cells are neither genetically mutated nor transformed neoplastic cells. However, it is supposable that this newly formed epithelial tissue still conserves its mesenchymal and stem cell features. If the insults are repetitive or persistent or chronic inflammation develops (secondary insult), as a consequence of recurring exposure to growth factors, cytokines, etc. the newly formed epithelium from MSCs, which still has conserved their mesenchymal features and stemness, go through rapid population expansion, and nullify their tumor suppressor genes, and consequently give rise to carcinoma cells, presenting EMT/MET markers, and aggressive behavior (Fig. 3G,H,I,J). Our hypothesis chains together other carcinogenesis theories such as the tissue organization field theory, the stem cell theory and the inflammation-cancer chain.

There are multiple lines of molecular and clinical evidence supporting this hypothesis. For instance, both colon and small intestine contain Lgr5+ multipotent stem cells, but cancer of digestive tract occurs preferentially in the colon and rectum, although epithelium turn-over is higher in small intestine [148]. These controversial observations could be explained fairly by the model we proposed. The repetitive injury and inflammatory milieu in colon attracts bmMSCs, which gives rise to colon epithelium and carcinoma consequently due to chronic induction of cytokines and growth factors. The same model can be applied to any carcinoma formation following chronic inflammation, such as Marjolin ulcer, Bladder SCC (following chronic schistozomia infection), hepatocellular carcinoma (HCC) (following chronic hepatitis and cirrhosis), non-small cell lung cancer (following chronic inflammation due to smoking), cervical cancer (following chronic HPV infection), and many other examples. Furthermore, this model easily describes carcinosarcoma formation and its monoclonality.

A more tangible evidence for our model is observed in kidney transplant patients. Squamous Cell Carcinoma (SCC) is a well-known complication in long term kidney transplant recipients [149]. Verneuil and colleagues have reported the presence of donor-derived epithelial cells in skin SCC and actinic keratosis [150]. In an attempt to further clarify the type of donor cell that has homed to these skin lesions, they observed donor-derived stem-cells in basal layers and invasive areas in all skin SCCs, but not in surrounding normal skin.

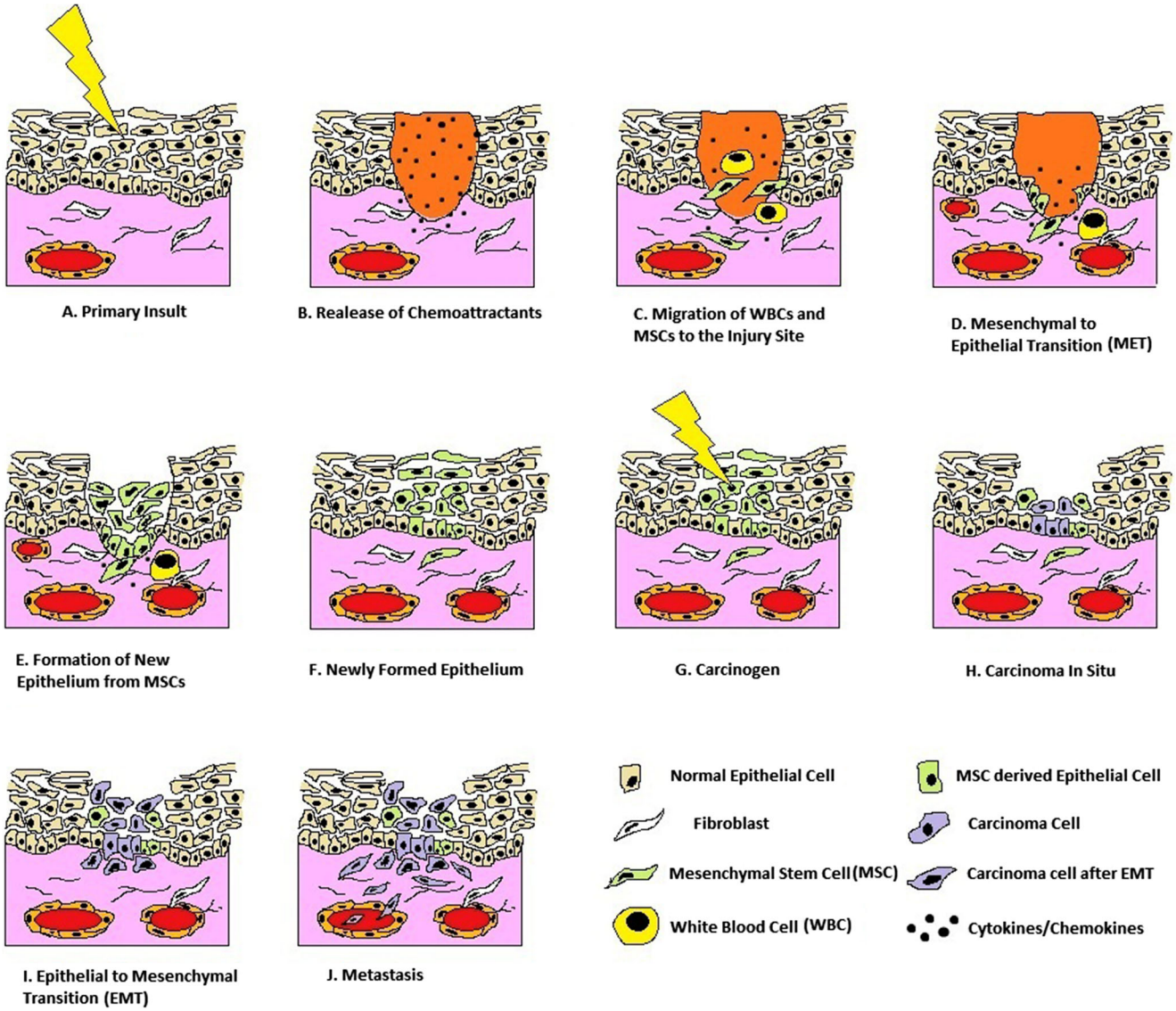

Fig. 3 Schematic diagram showing the process of carcinogenesis; (**a**). The primary insult causes disruptions in the epithelium and its basement membrane; (**b**, **c**, **d**). The injury attracts immune cells along with MSCs by means of chemokines and adhesion molecules; (**e**, **f**). MSCs pass through the injured basement membrane, enter the epithelial milieu and transdifferntiate to epithelial tissue (MET); (**g**, **h**, **i**, **j**); If the insults are repetitive or persistent or chronic inflammation develops (secondary insult), the newly formed epithelium from MSCs, which still has conserved their mesenchymal features, as well as their stemness, go through rapid population expansion, and nullify their tumor suppressor genes, and consequently give rise to carcinoma *in situ,* invasive carcinoma and metastasis

These donor-derived stem-cells expressed the EMT markers, vimentin, snail and slug in SCCs [151]. It is probable that the MSCs engrafted along with the kidney, had been hijacked by injured epithelium and their consequent transdifferentiation to and integration in the epithelium, creates a tissue with higher susceptibility to carcinogens (Fig. 3).

The role of chronic inflammation and the molecules involved in development of carcinomas has been studied extensively. Interestingly, some vague parts of these mechanisms can be enlightened by the model we proposed. For instance, the NF-κB pathway is one of the most fascinating links between inflammation and cancer formation and following its activation EMT regulators Snail and Slug are activated, which leads to downregulation of E-cadherin [152], and supposedly cell separation and cancer progression. However, inhibition of this pathway has been shown to enhance the growth of SCC and HCC [153, 154]. The progression of SCC and HCC following NF-κB pathway inhibition can be explained by our model, considering MSCs going through partial MET and giving rise to these carcinoma cells.

Another observation is in regard to Wnt/β-catenin pathway, which is supposed to play roles in EMT [155]. Vermeulen and colleagues showed that cancer cells with high Wnt pathway activity are observed near stromal myofibroblasts [156]. We can explain this observation by considering MSCs going through both MMT and MET, giving rise to both carcinoma

cells and myofibroblasts. In fact, EMT and MET are reversible processes, and observations are a snapshot *en route* to full EMT/MET and thus could not be representative of a precise epithelial or mesenchymal state [157] and considering the role of MET in carcinoma formation is as fair as EMT based hypotheses.

Conclusion

The high complexity and diversity in cancer development is still unraveled and through previous decades, cancer models have been re-written several times. In this paper, we presented a model of carcinogenesis which chains together the tissue organization field theory, the stem cell theory and the inflammation-cancer chain. In this model we propose that tissue resident stem cells could be leaked cells from bmMSC pool to various injured tissue, which consequently transform and integrate in the host tissue. If the insult persists or chronic inflammation develops, as a consequence of recurring exposure to growth factors, cytokines, etc. the newly formed tissue from MSCs, which still has conserved their mesenchymal features, as well as their stemness, go through rapid population expansion, and nullify their tumor suppressor genes, and hence give rise to neoplastic cell (both carcinoma and sarcoma, as well as carcino-sarcomas). Considering the probability of this hypothesis being true, the clinical and therapeutic use of MSCs should be with caution and careful surveys, and the recipients' long term follow-up seems to be insightful.

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Compliance with ethical standards

Conflict of interests The authors declare that they have no conflict of interest.

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