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Cancer Stem Cells in Metastasis Therapy

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Abstract

Tumors consists of subpopulation of cells in which each subtype has contributes to tumor progression. Specifically one subtype known as cancer stem cells are associated with the initiation, progression, resistance to conventional therapies and metastasis. Metastasis is leading cause of cancer related deaths. Overall it is important to consider cancer as a whole in which a mutated cell proliferating indefinitely and forming its hierarchy consisting of subgroups with different molecular signatures. To be able to target this disease we need to evaluate every step including initiation, progression, survival, angiogenesis and finally migration and repopulation. Cancer stem cells do play vital roles in each step however when metastasis can be stopped or eliminated we talk about saving a life or improving its quality. Considering how deeply these cancer stem like cells affect the tumor life and metastasis it is crucial to develop effective strategies against them. Metastatic cascade can also be directed by membrane derived vesicles specifically exosomes. Several studies show the role of exosomes in mediating cellular migration and pre-metastatic niche formation. During this chapter we wanted to explain in detail how the metastasis occur in tumor and how cancer stem cells contribute into the development of metastatic cascade and possibly suggest therapeutic approaches against cancer stem cells.

Keywords

Cancer stem cells · Metastasis · Cancer therapy

Abbreviations

CSCs	cancer stem cells
MMPs	matrix metalloproteinases
EMT	epithelial-to-mesenchymal transition
ALDH1A1	Aldehyde Dehydrogenase 1 Family Member A1
RTKs	receptor tyrosine kinases
MICs	metastasis-initiating cells
TICs	tumor-initiating cells
hWAPL	human wings apart-like
HPV	human papillomavirus
Pdcd4	programmed cell death protein 4
CXCL12	chemokine stromal cell-derived factor 1
VEGFR-1	vascular endothelial growth factor receptor 1
CDs	cluster of differentiation
CXCR4	chemokine receptor complex 4
CAFs	cancer associated fibroblasts
IGF-1	insuling growth factor 1

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IL-17A	interleukin 17A
DTC	disseminated tumor cell
MIF	migration inhibitory factor
RARRES3	Retinoic Acid Receptor Responder 3
NKX2-1	homeobox domain-containing transcription
MITF	microphthalmia-associated transcription factor
EVs	Extracellular vesicles
ABs	apoptotic bodies

1 Introduction

Tumor tissues are comprised of heterogeneous populations in which stem cells play important roles including the maintenance of the integrity of tissues. Since their discovery cancer stem cells are investigated deeply and thousands of studies have been done to target these stem like cells in cancer. Many therapeutical approaches that target those stem like cells hold promise in the fight of cancer. Heterogeneous tissue is composed of various subtypes of populations where cancer stem like cells exist in rare numbers but stay in quiescent state. Two distinct properties of these stem like cell population are the self-renewal capacity and differentiation into more mature and committed cells. Moreover stem like cells in tumor tend to cause more clonogenic and tumorigenic behavior overall. Interactions with stromal elements like fibroblasts and following various cascade of signaling events affect the stem cells physiology and may cause the initiation and continuation of tumors. Based on these knowledge cancer stem cell theory has been developed and studied for years. According to this, neoplasms are comprised of hierarchically organized cells and a group of cells called, cancer stem cells (CSCs) that may be the origin of initiation of the tumor, which can also recapitulate the entire tumor under favorable conditions.

CSCs are designated as the only subpopulation that are associated with tumor-initiation and they can also be responsible for the metastases. In a study done by Herman et al. it has been shown that CSC do play significant role in pancreatic tumor growth and they also present a side population of migrating stem like cells in the metastasis (Hermann et al. 2007). They finally concluded that CSCs may be the ones that initiate metastatic cascade.

Metastasis is a series of event where a circulating single or cluster of cancer cells detach from the primary tumor bulk by digesting extracellular matrix metalloproteins (MMPs) and through invasion reach the blood or lymphatic system and intravasation into the vasculature. In there, single or cluster of these cancer cells survive against harsh conditions of the blood and finally through extravasation leave the blood and settle into the final destination where a new colony will form. In this chapter we will focus entirely on the roles of CSCs in the metastatic cascade along with their association with the tumor microenvironment so called niche.

1.1 Stem Cells

Stem cells are special cells with potentials to self-renew and differentiate into other lineages in such conditions such as organ development and tissue repair. This mechanism is also being favored by cancer cells when needed.

In recent years a great effort has been made to be able to distinguish stem cells from non-stem cells. Especially in tumors it is very important to separate cancer stem cells in the population so that these cells can be targeted. Based on this many approaches such as differentiation and antibody directing therapies have been developed to target cancer stem cells. Presence or absence of certain markers were discovered and new ones are under investigation. But there is not a clear cut distinction between cancer stem cells and normal stem cells. However some markers are certainly more or less specific for different types of stem cells like the ones that separate embryonic stem cells from adult stem cells or pluripotent cells from progenitor ones. When it comes to cancer stem cells it is more difficult to distinguish them from non-cancerous stem cells due to the

presence of the same markers being expressed on both of the cell types. It is known that almost all the markers are expressed by normal stem cells as well as cancer stem cells therefore for scientists it is challenging to find new candidates as tumorigenic markers. Presently the ultimate choice for a therapeutic target depends on onco-fetal stem cell markers because they are not expressed on normal adult stem cells.

1.2 Cancer Stem Cells (Discovery and Its Origin)

The exact origin of CSCs is an unclear issue however hypotheses were recommend from time to time. Currently we know that there are three main hypotheses and the first one is the transformation of normal stem cells. The theory suggests that CSCs is transformed from normal stem cells, and through series of differentiation processes and accumulation of mutations they will contribute to cancer progression. These mutations are adequate enough to induce malignant transformation and bear tumor growth (Krivtsov et al. 2006; Scheel et al. 2011; Jordan 2009). While this theory encounters the clonal evolution theory, which indicates that all cancer cells have tumorigenic potential with a potential to recapitulate the entire tumor (Nowell 1988), development in the cancer stem cell field states that these two models share common mechanisms therefore it is suspense through which mechanisms one stem cell become cancer stem cell (Cabrera et al. 2015; Plaks et al. 2015). One can conclude that there is a dynamism in transformation of non-CSC to a CSC state, vice versa.

This transformation occurs very rarely and spontaneously and a variety of factors including inflammatory cell infiltration, chemokines and hypoxia can induce this event (Chen et al. 2016). Gaining stem cell characteristics also require signals from tumor niche (Pattabiraman and Weinberg 2014) as well as interactions amongst the cells within the tumor that might also regulate stemness of the tumor (Plaks et al. 2015). The former also is known as the second theory cancer stem cell in which of mature cancer cells dedifferentiate into cancer stem cells through a process called epithelial-to-mesenchymal transition (EMT) (Pattabiraman and Weinberg 2014). This transient state is critical not only for the survival of cancer cells, but also for metastatic progression. And the last hypothesis is the introduction of induced pluripotent cancer cells. Malignant transformation of adult stem cells into cancer stem cells were proposed by several researchers.

EMT is also another factor that affects the progression of cancer progression and eventual metastasis (Mani et al. 2008). During EMT cancer cells gain characteristics of normal stem cells including differentiation and self-renewal. Loss of polarity and cell-cell contact and alterations in the cytoskeletal structures cause cancer cells become motile and resistant to cellular death (Mani et al. 2008). These features allow CSCs to initiate new tumors that's why they are called tumor initiating cells (Reya et al. 2001). Up to date several surface markers were described as cancer stem cell markers including; CD44, CD24, CD34, CD133 and CD117, and Aldehyde Dehydrogenase 1 Family Member A1 (ALDH1A1) (Gottschling et al. 2012). Various signaling pathways and growth factor receptor tyrosine kinases (RTKs) induce EMT. One of the most important signaling pathway proteins is Transforming Growth Factor beta (TGF-β). It is the most and widely studied protein and it has been shown that TGF β phosphorylate and activate Smad2a and Smad3 which in turn form trimers with Smad4 and cause a translocation to the nucleus for the regulation of TGF-β target genes (Fuxe et al. 2010). Other proteins like Notch and Wnt also are collaborated with TGF-β to induce EMT (Shin et al. 2010; Eger et al. 2004; Timmerman et al. 2004). As major regulators of EMT SNAIL, SLUG, TWIST and ZEB transcription factors are well characterized and studied (De Craene and Berx 2013). When activated these factors can suppress epithelial markers like E-cadherin and upregulate mesenchymal markers such as N-cadherin and vimentin. Activation of other signaling molecules like

Ras/Raf/MAPK, PI3K/Akt can aid these processes (Valcourt et al. 2005; De Craene and Berx 2013).

It has been more than 50 years of research since the discovery of cancer stem cells based on the similarity between cancer and embryonic development processes. Throughout these years a number of tumors were found to be associated with cancer stem like cells as a driving force. Tumors that may contain the traces of cancer stem like cells include leukemia (Bonnet and Dick 1997) and solid tumors such as bladder cancer (Chan et al. 2009), breast cancer (Al-Hajj et al. 2003), malignant melanoma (Schatton et al. 2008), ovarian cancer (Zhang et al. 2008b), head and neck cancer (Prince et al. 2007), pancreatic cancer (Hermann et al. 2007), Central Nervous System (CNS) cancers (Singh et al. 2004), colon carcinoma (Dalerba et al. 2007), liver cancer (Zhang et al. 2008b), Ewing sarcoma (Suva et al. 2009), and chordoma (Aydemir et al. 2012). The primary studies based on hematological diseases show that a subset of cells found in the tumor heterogeneity drive the tumor development and relapse.

Unlike liquid tumors it is very challenging to detect cancer stem cells in solid tumors due to loss of specific markers present in cancer stem cells. Among specific markers CD133 is the one very speculative in which colorectal carcinoma studies indicate that CD133 negative colorectal cancer stem cells recapitulate the entire tumor. (Shmelkov et al. 2008; Ren et al. 2013).

Several analytical methods and approaches have been developed to detect and characterize CSCs. Most used techniques for detection and isolation CSCs are functional, molecular, and cytological and filtration approaches as well as functional methods and ultimately xenotransplantation studies hence animal modeling. Assays such as colony and sphere formation, side population analysis, aldehyde dehydrogenase activity and drug therapy resistance are being practiced regularly to distinguish cancer stem cells from non-CSCs. Innovative techniques like cell sorting based on magnetic capturing of fluorescent conjugated antibodies based on certain cell surface proteins pioneered a new era in the scientific world. With this technology it became possible to separate CSCs from non-CSCs among heterogeneous cell populations in a more reliable way. (Kentrou et al. 2011; Greve et al. 2006).

In addition to these techniques gene expression analysis by multiplex reverse transcription quantitation, immunocytochemistry, immunohistochemistry and immunofluorescence are the common molecular methods to characterize CSCs. (Lianidou and Markou 2011) As for functional assays the gold standard one is xenotransplantation into immune-deficient animals in which cancer stem cells being transplanted into immune-deficient animal and let them reform the original tumor. (Fulawka et al. 2014) All of these techniques and cons and pros based on their set up but the better and more reliable method is to combine them appropriately. Overall functionally CSCs are defined by their capability to begin tumors in immune-compromised/deficient mice upon serial injections which is the indicators of self-renewal, differentiation into multilineages to form the tumor entity. (Korkaya et al. 2008; Ginestier et al. 2007).

1.3 Cancer Stem Cells in Metastasis

In 1889 Paget proposed the hypothesis of Seed and Soil, which is coherent with the CSC model [45]. In his hypothesis, a CSC is the seed where it is nourished by the soil known as the metastatic site. This new environment is the niche where the growth of CSCs will be promoted. Epigenetic and genetic alterations will also take place to lead CSCs drive the tumor and these changes ultimately affect the phenotype of the primary tumor. So the new metastatic tumors are known to arisen from the CSCs. Based on a colorectal cancer model Brabletz et al. suggested that tumor entity possesses a heterogeneous bulk where part of cells play roles in proliferation and cell cycle arrest where others in epithelial to mesenchymal transition, cell adhesion and spread. He further proposed that all of these events are orchestrated to push for tumor progression by a subset of cells called “migrating cancer stem cells”(Brabletz et al. 2005).

Metastasis is a multistep process that begins with the invasion of cancer cells to nearby tissues locally. These metastasis-initiating cells (MICs) are able to seed clinically important metastatic colonies in other organs and tissues of the body. Like the tumor-initiating cells (TICs), MICs can take over some of the normal stem cell pathways, increase cellular plasticity and stem-ness. MICs also must hold additional competences which will allow them to survive the metastatic cascade and act as TICs in an organ microenvironment characteristically different from the primary tumor. These cells are exceptionally difficult to identify, capture, and characterize but they certainly create a relationship between the primary tumor and following metastasis. Even the source of MICs remains indefinable; they might occur at the primary tumors or appear later in the metastatic cascade or even acquire features when reach to final destination. MICs share common characteristics with cancer stem cells therefore tools to analyze and identify cancer stem cells are also used for MICs including *in vitro* tumor sphere assays, in vivo dilution tumor initiation studies, analyzing cancer stem cell (CSC) cluster of differentiation (CDs) markers (Celia-Terrassa and Kang 2016).

Malignant tumor cells first lose their cell-cell adhesion capacity and detaches from the primary tumor bulk. Through alterations between cell and their extracellular matrix interactions, cells find their way to invade the adjacent stroma, a process called invasion. Basement membrane and extracellular matrix are degraded by substances in addition with the expression as well as suppression of proteins associated in motility and migration (Cooper et al. 2003). In a breast cancer study done by Dustin et al. nuclear translocation was found to be a major rate limiting factor for CSC spreading. They further suggested that cytoskeletal elements like myosin IIB, which was upregulated in CSCs, might targeted against cancer stem cell dissemination from the primary tumor site (Thomas et al. 2016). One of the cancer stem cell characteristics, pluripotency was shown to decrease in cervical tumor spheres after knockdown with human wings apart-like (hWAPL) and human papillomavirus (HPV) indicating that suppression of hWAPL expression decreased HPV E6 levels and consequently inhibited tumor invasion in mice suggesting that hWAPL is a cervical CSC marker for proliferation and a promising target for therapeutics (Gong et al. 2017). CD133 and CD44 are discovered surface markers for the identification of colorectal cancer stem cells (O'Brien et al. 2007; Chu et al. 2009). It was shown that expression of both of these markers were found to be associated with liver metastasis in colon cancer patients (Jing et al. 2015). In a similar study done by Jiang et al. gastric cancer stem cells positive for CD26 and chemokine receptor 4 (CXCR4) were involved in invasion and metastatic ability (Jiang et al. 2017).

Next, cells must reach the nutrient and oxygen through a step called angiogenesis so that growing cancer cells will be nourished their toxic waste will be removed (Ellis and Fidler 1996). Cancer stem cell phenomenon clashed with the hypothesis of angiogenic behavior of tumor bulk as different parts of it show variety in levels of oxygen. This was shown by Folkman et al. that heterogeneous population of human liposarcoma cells reflect the angiogenic capacity variously when implanted into mice such that one subpopulation (so called cscs) give rise to highly angiogenic whereas others (non-cscs) develop poorly angionegnic tumors or even non angiogenic (Achilles et al. 2001). A different study has shown that the reason for tumor relapse and metastasis is linked to cancer stem cells (CSCs), under control of numerous mechanisms like elevated levels of angiogenesis (Folkins et al. 2009).

Intravasation is the step where cancer cells enter into circulatory system and survive in it. In a study investigated by Asangani et al. post-transcriptional regulators such as miR-21 plays in important role in invasion or intravasation by regulating and targeting programmed cell death protein 4 (Pdcd4) in colorectal cancer (Asangani et al. 2008). In the blood invaded cells resist despite the harsh condition such as high blood pressure rate and platelets by interacting with endothelial cells forming stronger bonds and by penetrating the base membrane and endothelium leaves the blood vasculature at a distant organ by extravasation (Chay et al. 2002), finally settle into

the new environment and build its colony (Chambers et al. 2002; Wirtz et al. 2011). Adaptation of the cells into new site is driven by CSCs (Reya et al. 2001; Tu et al. 2002).

Since CSCs have self-renewal and clonogenic capabilities they are more likely to develop metastatic behavior. In deed CSCs present a varying degree of motility and invasion Moreover, CSCs should have some degree of motility and invasion to spread a distant site (Brabletz et al. 2005). Based on the similarity in the migration of normal stem cells and cancer stem cells, it has been recently suggested they share a same mechanism, which is upregulation of the chemokine stromal cell-derived factor 1 (CXCL12) and its G-protein-coupled receptor CXCR4 (Kucia et al. 2005). Previous studies proposed that hepatocyte growth factor (HGF) and its receptor MET have a parallel function in driving the recruitment and migration of normal stem cells together with cancer stem cells. In the embryonic term, MET in response to HGF expression causes a migration of embryonic cells for a successful development as similarly observed in adults where bone marrow stem/progenitor cells (Andermarcher et al. 1996; Bladt et al. 1995; Takayama et al. 1996) express MET in response to HGF gradients to wounded tissues for repair. Upto date, it is not for certain that the overexpression of MET expression is associated with CSCs. However, according to the theory of stem cell plasticity caused by the malignant transformation of normal stem cells if cancer stem cells originate from the malignant transformation of normal stem cells, we can accept the fact that MET expression might enable CSCs to shift to the invasive program (Pardal et al. 2003; Reya et al. 2001). MET has been known as an oncogene and this brings with a dual role as in the initiation as well as clonal selection. It also has been proposed that independent of the oncogenic events wild-type MET can enhance motility, invasion and metastasis of CSCs (Lorenzato et al. 2002). When MET is overexpressed it causes cells to become sensitive to HGF and invasive signaling so that microenvironment can promote metastasis (Mueller and Fusenig 2004). When other oncogenes including Ras, RET, and ETS become activated and together with other mitogenic signals stimulating MET transcription (Boccaccio et al. 1994; Gambarotta et al. 1996; Ivan et al. 1997) occur, MET overexpression is considered as a consequence however it absolutely has a key role in cellular metastasis.

1.4 Tumor Niche and Cancer Stem Cells

The tumor microenvironment is embed in a non-cellular matrix and comprised of non-cancerous cells including fibroblasts, immune cells, endothelial cells. These components build the tumor stroma which alters as tumor progresses and grows and eventually become drug resistant (Egeblad et al. 2010; Junttila and de Sauvage 2013). Tumor niche nourishes the cancer stem cells by releasing a variety of factors that will protect them immune attach and keep their plasticity maintaining their properties (Lloyd et al. 2016). As for metastatic preference certain growth factors are begin released by tumor stroma for the direction of the primary tumor cells to the secondary tumor site as in the case of cancer associated fibroblasts (CAFs) in the primary breast cancer secreting CXCL12 and insuling growth factor 1 (IGF-1) which will stimulate bone metastasis (Zhang et al. 2013; Zhang et al. 2009). In a similar example, CAFs secrete hepatocyte growth factor that will stimulate CSCs to self-renew promoting the reprogramming of colorectal cancer progenitor cell into CSCs through the signaling of β-catenin pathway (Vermeulen et al. 2010). After chemotherapy treatment certain cytokines specifically interleukin 17A (IL-17A) is being released that contributes self-renewal trait of colorectal CSCs promoting invasion (Lotti et al. 2013). This is an indication of how chemotherapy re-shape the tumor niche and aid tumor progression therefore tumor microenvironment might be altered as chemically (Zeuner et al. 2014).

2 The Role of CSCs in Modulating the Tumor Microenvironment Through Secretion of EVs

It has been known for long that during apoptosis cells release vesicles to the extracellular environment. Comprehension of healthy cells secreting the similar vesicles is also considered currently by the researchers and they used the generic term for these vesicles as extracellular vesicles. Extracellular vesicles (EVs) contain at least three sub-classes namely exosomes, microvesicles (MVs), and apoptotic bodies (ABs). Exosomes are made by budding of endosomal membrane inwardly, while microvesicles (MVs) are formed by budding directly from the plasma membrane. Apoptotic buddies, on the other hand, are made during programmed cell death. Their size, structures and functions are being evaluated consistently. Origin of EVs whether derived from normal cells or cancer cells differ in molecular markers which will affect the function of it in the recipient cells. Differences in molecular signatures of these EVs may help in diagnosis as well as prognosis in a variety of cancers. Exosomes have a distinctive role as a cargo during cell to cell communication in which they carry almost any molecule. In cancer through exosomes cells contact one another which will aid in metastasis, drug resistance and even immunology (Milane et al. 2015). In a study done by Ono et al., increased expression miR-23b and decreased expression of MARCKS were found in bone marrow of a metastatic breast cancer patient suggesting that exosomal transfer of miRNAs from the bone marrow might be endorsing breast cancer cell latency in a metastatic environment (Ono et al. 2014).

Exosomes are carried from original cells to final destination through the circulatory system and localized there by binding to cell surface through their membrane proteins that will be recognized by the recipient cells. Taylor et al., showed that greater levels of exosomes were found in body fluids of cancer mouse models and cancer patients (Taylor and Gercel-Taylor 2008; Ghosh et al. 2010). Exosomes play active roles in cancer progression. Studies indicate that exosomes derived from mesenchymal stromal cells (MSC) or fibroblasts secrete various miRNAs and soluble factors which were delivered into tumor cells that enable cancer progression and cause drug resistance in several cancers including multiple myeloma, colorectal cancer, and gastric cancer cells (Roccaro et al. 2013; Hu et al. 2015b; Ji et al. 2015) advantaging tumor survival and growth. Cancer cell-derived exosomes can favorably fuse with the cells to form a pre-metastatic niche for metastasis (Hoshino et al. 2015). Also these cancer derived exosomes may turn normal epithelial cells into cancerous cells as shown in murines (Melo et al. 2014). Taken together, exosomal delivery to drive tumorigenesis is a very common and popular field of interest that capture researchers' attention for not too old. Exosomal delivery of therapeutics even became popular in cancer treatment (Seow and Wood 2009; Camussi and Quesenberry 2013).

Exosomes derived from cancer stem cells drive an activated angiogenesis, which will lead stimulation of normal endothelial cells to grow and form vessels resulting metastasis and tumor progression (Grange et al. 2011). Mesenchymal stem cells facilitate EMT and induce stem like properties which will allow cancer stem cells to increase survival in the circulatory system. The role of CSC derived exosomes in metastasis is that they cause tumor reseeding and pre-metastatic niche formation similar to MSC-derived exosomes. For instance in a study done by Wang et al., gastric cancer (GC) MSC-derived exosomes were detected to transport miR-221 to HGC-27 cells aiding proliferation and migration (Wang et al. 2014).

3 Organ Specific Metastasis

Tumors can prefer specific organs depending a number of factors. This selection of metastasis to certain organs is called organotropism (Tayyeb

and Parvin 2016). There are two main hypotheses that might enlighten organotropism one being an anatomic circulation system, which is tumor cells spread into lymphatic system and followed by a distant spread by the vascular system (Hess et al. 2006). The first hypothesis is logical but does not explain all that metastatic patterns of certain cancers in the body. According to the first hypothesis liver and brain take same amount of blood in volume but differ in metastatic patterns (Obenauf and Massague 2015; Budczies et al. 2015). This leads the scientific world to question whether other possible mechanism might have a role in selection organs to metastasize. The second hypothesis lays underneath the "seed-and-soil hypothesis" which, indicates that metastatic tumor cells can be fed and grow only in accepting tissues with organ-specific "soils" [78]. In this regard we can conclude that metastatic preference is a combination of spreading of tumor cells through vasculature and lymphatic system and also circulating tumor cells (CTCs). In this chapter we will focus more on CSC which share similar features with EMT and CTCs (Kasimir-Bauer et al. 2012; Sun et al. 2011).

3.1 Metastasis to Bone (s12943)

The study done by D'Amico et al. indicates that breast CSCs-like have a tendency to metastasize bone with a mesenchymal and migratory $CD44^+$ $CD24^-$ phenotype suggesting that breast CSCs favors the bone as a soil to metastasize (D'Amico et al. 2013). This migration is supported by vascular endothelial growth factor receptor 1 (VEGFR-1) expressed by the bone marrow-derived hematopoietic progenitor cells to form clusters and fibronectin (Kaplan et al. 2005). Osteogenic environment also induces colonization by adherens junctions like osteogenic N cadherin E-cadherin derived from cancer cells and ultimately initiate mTOR pathway and additional oocyte secretion of factors including CCL5, MMP and extracellular ATP (Sottnik et al. 2015) promote tumor progression (Wang et al. 2015).

Presence of the recognized stem/progenitor cell ($CD44^+CD24^-$) subpopulation is primary found within the disseminated tumor cell (DTC) component in bone marrow by Balic et al. In their study they showed that breast cancer stem cell phenotype was described as CK+ in all of their patients. It has been known that majority of the patients with DTC may have a lifetime risk for relapse (Dearnaley et al. 1991).

3.2 Metastasis to Liver

Usually cancer cells that migrate to liver as a metastatic site are not known as liver cells rather different parts of the body where the primary tumor initiated. Metastatic liver cells are considered to cause the advanced stage of the tumor. As for migration tendency hepatic stellate cells are known to play significant roles in preparing the pro-metastatic environment (Eveno et al. 2015). In a recent study done by Nielson, secreted granulin by macrophages excites hepatic stellate cells to release of periostin so that fibrotic niche in the liver provides metastasis (Nielsen et al. 2016). Studies indicate that subpopulation of $CD26^+$ cells present in the primary and metastatic tumors in colorectal cancer patients cause liver metastasis suggesting that $CD26^+$ CSCs indicate greater potential for invasion and migration (Pang et al. 2010). In a similar study done on colon cancer patients that has $CD133^+/CD44^+$ genotype seem to possess metastatic properties to liver (Bellizzi et al. 2013). Other subpopulations including $CD133^+CXCR4^+$ may increase the tendency to metastasize to liver and cause reduced two-year survival rate in colon cancer patients (Zhang et al. 2012). A expressional correlation between $CD133^+$ (Horst et al. 2009) and Nanog (Ibrahim et al. 2012), which are important cancer stem cell markers, in colorectal cancer cells are found to be involved in the liver metastasis (Xu et al. 2012). Inhibitory factors such as macrophage migration inhibitory factor (MIF) also play roles in stimulating hepatic cells to be migratory, proliferative and apoptotic resistant in colorectal cancer cells (Hu et al. 2015a).

Colonization of colorectal cells in the liver are induced by accumulation of soluble factors like angiopoietin-like 6 protein in hepatic blood vessels (Marchio et al. 2012).

3.3 Metastasis to Brain

Brain metastases were thought be associated strongly with astrocytes (Barros et al. 2014). It has been known that astrocytes are part of the brain microenvironment and do play and important role in facilitating metastasis. Secretion of IL-23 from astrocytes upregulates the MMPs specifically MMP2 to improve the metastasis of melanoma cells to brain (Klein et al. 2015). An important study has been done by Lin Zhang et al. who demonstrated that astrocytes cause loss of PTEN in tumor cells by secreting exosomal miRNA leading a permissive metastatic microenvironment for cancer cells. In their study they showed that signals that from the brain niche are received by cancer cells causing the secretion of chemokines especially one named CCL2 stimulating development mechanistically, cancer cells receive signals from the brain microenvironment that lead to metastatic cells (Zhang et al. 2015).

Besides these extracellular factors generated from brain microenvironment other cellular effects take place in the brain metastatic cascade. Tumor initiating cells share a common mechanism with the metastasis (Croker and Allan 2008). Only very few amount of cells that are shed from the primary tumor can survive in the vasculature system, metastasize and form their colony as the secondary tumor (Kienast et al. 2010; Luzzi et al. 1998). Studies have described CSCs being involved in the increased adhesion, migration, invasion and development of metastases (Croker et al. 2009; Liu et al. 2010; McGowan et al. 2011; Davis et al. 2010). The presence of cancer stem cells and metastasis in lung tumor led idea that metastasis to brain from lung might be involved in cancer stem cells (Nolte et al. 2013). In that study Sara et al. showed that brain metastases from lung presents cells having self-renewal and sphere forming capacities, which are CSC properties.

Cancer stem cells are found to act in an organ specific manner to lead tumor cells for metastasis to brain. Okuda et al. shows that CSCs characterized with a CD24−/CD44+/ESA+ genotype from metastatic breast cell lines are significantly more metastatic than non-CSC populations. They reasoned this by conclusion of lower level of miR-7 which targets and inhibits an induced pluripotent stem cell marker, KLF4 expression causing significantly and inversely correlation to brain but not bone metastasis in animal models (Okuda et al. 2013).

3.4 Association of CSCs in Metastasis Therapy

Heterogenic subpopulation specifically called CSCs is measured based on the ability to seed tumors at limiting dilutions in animal models. Enriched cell populations by CSC also display certain properties in vitro. For instance, CSC-enriched subgroups can be isolated with cell-surface markers as described previous stem cell based studies (Al-Hajj et al. 2003; Li et al. 2007; Ricci-Vitiani et al. 2007; Singh et al. 2003; Zhang et al. 2008a). As an example breast CSCs are enriched in the $CD44^{+}/CD24^{-}$ side populated cells (Al-Hajj et al. 2003). Another property CSCs has is their ability to form sphere or tumor-spheres in CSC-enriched tumor cells (Dontu et al. 2003). Lastly, CSC-enriched populations are highly resistant to conventional therapeutics and ionizing radiation CSC-enriched populations exhibit increased resistance to chemotherapeutic agents (Bao et al. 2006; Dean et al. 2005; Diehn and Clarke 2006; Eyler and Rich 2008; Li et al. 2008; Zhang et al. 2008a) and ionizing radiation (Diehn and Clarke 2006; Woodward et al. 2007).

Available treatment methods could be possibly improved by targeting CSCs to reduce the possibility of recurrence and metastasis. Automated screening technologies are found to be enabling the identification of agents that kill CSCs. Due to its heterogenic structure of tumor bulks one can not selectively kill only CSCs since they only comprise a small portion of the entire population. Therefore

standard cell viability assays should not be applied to tumor as a whole and only CSC-specific toxicity should be identified. As long as highly enriched populations of cancer stem cells are screened then one can surely target cancer stem cells who are known to be responsible for initiation and progression of the tumor. Although selective treatment seems promising it is not applicable for current solid tumors since cancer stem cell enrichment is lost in vitro culture as shown by Fillmore et al. during breast cancer stem cell studies (Fillmore and Kuperwasser 2008).

In 2008 Mani et al. showed that EMT in normal as well as cancer with epithelial origin causes the enrichment of cells with stem-like features (Mani et al. 2008). In their study Gupta et al. sowed that extrinsically induced EMT led increase in drug resistance. They further applied a chemical screening to assess novel therapeutic agents causing toxicity on selected cell populations. They concluded that new agents to target breast CSCs selectively was possible (Gupta et al. 2009).

Loss of differentiation ability, which is a typical stem cell characteristic leads to de-differentiaiton phenotype and ultimately stem cell-like traits associated with metastasis (Cao et al. 2014). In a related study done by Morales et al. Retinoic Acid Receptor Responder 3 (RARRES3) might be potential biomarker and when downregulated it caused a suppression in lung metastasis from breast cancer and considered as an differentiation (as adjuvant) therapy promoting tumor differentiation (Morales et al. 2014). Induction of dedifferentiation and stem cell-like properties aids in promoting lung metastasis so by loss of homeobox domain-containing transcription NKX2-1, a lung lineage-specific transcription factor lung adenocarcinoma, genetically leads an increase in metastatic seeding (Winslow et al. 2011). Li et al. showed that in parallel with other factors like lineage-specific transcription factors (FOXA2 and CDX2), NKX2-1 repressed lung metastasis (Li et al. 2015). It is very crucial to target lineage cell fate related genes since they promote differentiation and inducing stem cell characteristics that promote lung metastasis. In a very similar study done by Cheung et al. two differentiation transcription factors named GATA6 and HOPX synergistically work as inhibitors of metastatic progression (Cheung et al. 2013). Another differentiation factor found to be lost in melanoma is microphthalmia-associated transcription factor (MITF) so targeting this pathway might benefit in the design of new melanoma therapies (Cheli et al. 2011).

4 Future Perspectives

Metastasis related death is the major challenge in cancer therapy. Therapies targeting tumor initiation, progression and finally metastasis were investigated and novel methodologies were developed in years however there is still a long way to go against cancer battle. CSCs play crucial roles in aiding throughout the tumor progression journey beginning from the initiation to the final step, metastasis. Targeted therapies against CSCs require a thorough enrichment in CSC in the tumor bulk. Combinational therapies against genes regulating every step of metastasis and corresponding stem cell markers might be targeted synergistically to improve the these approaches.

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