Cancer Stem Cells: A Cause or A Consequence of Field Cancerization

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Metastatic tumor progression is a sequential process involving local invasion of cancer cells into the adjacent normal tissue followed by their intravasation, survival in the circulation, subsequent extravasation and colonization at a distant site from the primary tumor. In recent times, metastasis has been viewed as a process which involves a dynamic crosstalk between genetically/epigenetically modulated cancer cell types and their activated but nonmalignant stromal components. It is not only the survival benefit of dysregulated cancer cells, but also the support provided by the tumor adjacent stromal microenvironment that determines the occurrence of successful metastasis. Recently, a considerably significant role of cancer stem cells (CSCs), with tumor initiating and recapitulating properties, has been anticipated in metastatic spread of tumor. Till date, the underlying mechanisms and factors responsible for generation of CSCs have not been well understood. In general, CSCs are speculated to reside in niches, which are histologically distinct regions within the tumor microenvironment. These niches help in maintenance of the principle properties of CSCs, preserve their phenotypic plasticity, protect them from the immune system and facilitate their metastatic potential [1, 2]. The CSC niche seems to play an essential role in maintenance, functioning, self-renewal and expansion of CSC by providing spatially and temporally coordinated signals originating from cellular component consisting of fibroblasts, endothelial cells, mesenchymal stem cells, immune cells, vasculature and extracellular matrix proteins [3, 4].

Some possible interactions between CSCs, non-stem cancer cells and stromal cells have been described via a variety of soluble factors including growth factors, cytokines and chemokines which directly or indirectly help in maintenance of CSC number as well as influence the local microenvironment in several ways to exert a broad range of effects on tumor progression. The primary tumor-derived CSCs, on the other hand, generate their progenitors and terminally differentiated cells (i.e. clones of bulk cells) with phenotypic and functional heterogeneity at different tissue levels.

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Likewise, various secreted regulators in the primary tumor microenvironment transform the adjoining normal stroma. The sequential changes occurring at broader tissue level, beyond localized areas of primary tumor development, are considered under the preview of ‘field cancerization’. Although, the field cancerization theory has been regularly updated to involve both the stromal and epithelial component in tumor progression, yet it fails to describe the role of epithelial component in this process. New evidence has now emerged suggesting a key interaction between mammary epithelia and the adjacent tumor stroma, which is changing the way breast cancer is perceived. A distribution pattern of CSCs in primary breast tumor, tumor-adjacent and/or tumor-distant tissues have recently been observed by our group with a possible association of generation of CSCs and field cancerization (unpublished personal communication). The findings suggest that both the field cancerization phenomenon and process of generation of CSCs seem to be interconnected, possibly mediated by cues received from either CSCs or CSC niche, which has also been described elsewhere [5, 6]. Tumor cells as well as stromal cells both release signals that activate the surrounding cells, induce expansion of stroma. Especially, the interaction at tumor front can result in distinct migratory signals which further helps in inducing metastasis. Besides, cancer associated fibroblasts (CAF) have been associated with neo-vascularization and growth promotion. Their association with enhanced invasiveness of tumor cells, possibly through induction of Epithelial to Mesenchymal transition (EMT) is also well established [7]. Interestingly, several reports suggest that factors secreted by CAFs induce loss of E-cadherin along with augmented motility and these molecular factors are potent inducers of EMT. Further, the interaction between cancer cells and stromal cells could initiate a complex signaling cascade, thus helping in enrichment of CSCs and initiation of field cancerization [8]. Whereas, these signals come from CSC niche, which itself is very dynamic as it may be a resultant of either CSCs themselves explicitly helping in formation of the niche by producing various factors that pass signals between CSCs and stromal cells or the CSCs utilizing the pre-existing tissue-specific stem cell niche. Taken together, these factors are
anticipated to encourage tumor progression and assist in maintenance of CSCs & CSC niche. Both cancer cell and fibroblast-derived molecules carry a set of regulatory molecules, including proteins and different species of RNA, which cooperatively support field cancerization and metastatic tumor spread.

In conclusion, the complex molecular crosstalk between CSCs, cancer cells and fibroblastic cells seem to play key roles from the early steps of niche formation, through local invasion to metastatic growth, and finally metastasis initiation. The prominent role of crosstalk between CSCs and CSC niche in the metastatic cascade is well justified by the effect of CSC-derived secretory molecules on the non-malignant cells, defining steps of CAF differentiation and regulating precursor cell functions in niche construction. Furthermore, the local CSC niche can also be important in CAF heterogeneity possibly attributed to tumor-stroma co-evolution and potential paracrine communication(Figure) Finally, the involvement of CSCs and its niche in multiple processes of cancer progression and local invasion into adjacent normal tissue indicates its major role in field cancerization, suggesting the cancer stem cells to be the ‘cause’ rather consequence of ‘field cancerization’.

References