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REVIEW ARTICLE

# Cancer Stem Cells: Innovative Approach for Testable Alternatives against Therapy Resistant Cancer

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ABSTRACT

Chemo-resistant cancer stem cells represent a sub-population of cancer initiating phenotype in primary cancer. These cells evolve in to a metastatic phenotype via activation of multiple cell signaling pathways for cancer cell survival and epithelial-mesenchymal transition. Reliable cancer stem cell models represent a valuable experimental approach for drug discovery platform to identify efficacious testable alternatives against therapy-resistant cancer. Present commentary provides a systematic discussion of relevant conceptual and technical aspects of cancer stem cell biology and its significance for therapeutic alternatives.

**Introduction:** Progression of early stage cancer to advanced stage metastatic disease represents a major cause of death [1]. Treatment options are dependent on cancer subtype specific pathology and status of hormone/growth factor receptors. Therapeutic options include mainstream conventional chemotherapy comprising of multi-drug combinations and targeted therapy using pathway selective small molecule inhibitors [2]. Major limitations of conventional chemotherapy or targeted therapy include long-term systemic toxicity, spontaneous/acquired therapy resistance and emergence of drug-resistant cancer initiating premalignant stem cell population. In addition to sporadic cancer, genetically predisposed cancers that carry germline mutations in tumor suppressor genes BRCA-1, BRCA-2, P53 and APC, and in DNA mismatch repair genes MLH1, MSH-2 and MSH-6 [3,4], represent formidable challenges for appropriate therapeutic intervention. Collectively, these limitations have negative impact on therapy response and thereby, represent an unmet need for identification of efficacious stem cell targeting therapeutic alternatives.

In integrative oncology naturally-occurring dietary phytochemicals and nutritional herbs have been widely used for general health issues and palliative treatment for cancer. Traditional Chinese medicine has documented use of nutritional herbs in women for estrogen-related health issues including breast cancer [5, 6]. Human consumption, low systemic toxicity and documented preclinical mechanistic leads for efficacy provide scientifically robust rationale for investigations focused on natural products as testable therapeutic alternatives.

Present commentary discusses recent publications [7-10] that describe development of stem cell models for breast and colon cancer, and discuss potential significance and mechanistic leads for identifying nontoxic efficacious natural products as testable alternatives against therapy-resistant cancers.

**Stem Cell Models:** Stem cell population plays important role in regulating normal cellular homeostasis and tissue regeneration in all epithelial organ sites. Cell signaling pathways such as Wnt/β-catenin, Notch and Hedgehog are responsible for maintenance of the normal stem cell population [11]. Cancer stem cells represent a subpopulation of chemotherapy-resistant cancer initiating premalignant cells intrinsic to primary cancer. In cancer stem cells the normal regulatory pathways are disrupted, and signaling pathways for cancer cell survival are activated. These activated pathways facilitate signaling via RAS/BRAF/MEK/ERK, PI3K/AKT and m TOR pathways that provide growth advantage to the cancer cell phenotype [12-16].

Reliable cellular models for cancer stem cells facilitate mechanism-based investigations to identify efficacious testable alternatives against therapy-resistant disease. Drug-resistant cancer stem cell models have been developed and characterized for molecular subtypes of clinical breast cancer and for genetically predisposed colon cancer [7-10]. The therapeutic agents to select resistant phenotypes include estrogen receptor modulator, EGFR/HER-2 inhibitor and DNA synthesis inhibitor for breast, and non-steroidal anti-inflammatory drug, and DNA synthesis inhibitor for colon.

Developed breast cancer stem cell models are relevant to the clinical Luminal A, HER-2-enriched and triple-negative breast cancer subtypes, while colon cancer stem cell models are relevant to genetically predisposed familial adenomatous polyposis (FAP) and hereditary non-polyposis colon cancer (HNPCC) subtypes. It is notable that genetic defects that characterize FAP and HNPCC subtypes, are also detected in sporadic colon cancers [3, 4].

**Stem Cell Markers:** Cell surface proteins including cluster of differentiation CD44 and CD133, and select nuclear transcription factors including octamer-binding factor-4 (OCT-4), Kruppel-like factor-4 (Klf-4), sex determining region box Y-2 (Sox-2), cellular Myc (c-Myc) and DNA-binding transcription factor (NANOG) exhibit upregulated expressions in the stem cell population. The transcription factors, OCT-4, Klf-4, SOX-2 and c-Myc are also essential for the maintenance of induced pluripotent stem cells [3, 4]. Several transcription factors exhibit positive correlation with clinical progression of breast cancer [12, 13, 16]. These aspects provide evidence for sensitivity and specificity of these molecules as stem cell specific markers.

Drug-resistant hyper-proliferative breast and colon cancer stem cells exhibit increased tumor spheroid formation. At the molecular levels these cells exhibit upregulated expressions of CD44, CD133, OCT-4, NANOG and c-Myc, relative to the drug-sensitive phenotypes [8-10]. .

**Natural products and cancer stem cells:** Cancer preventive efficacy of natural products including dietary phytochemicals and their constituent bioactive compounds polyphenols, flavones, terpenes, micronutrients, vitamins A, C and E, and Chinese nutritional herbs and their constituent bioactive compounds has been well documented in preclinical models of organ site cancers. This evidence has recently been extended to cancer stem cells [17-20].

In the lapatinib resistant stem cell model for HER-2-enriched breast cancer naturally-occurring terpene and endogenous metabolite of vitamin A effectively downregulate the stem cell markers. Similarly in the sulindac-resistant stem cell model for colon cancer curcumin and vitamin A derivative are effective [7-10].

**Future Perspectives:** It needs to be recognized that in vitro preclinical data generated from established cell lines, as well as those from animal models are dependent on extrapolation for their clinical translatability. This limitation emphasizes alternative experimental approaches. In this regard, experimental approaches using patient-derived tumor xenograft models [21] or patient-derived tumor organoid models [22-24] are likely to provide scientifically robust rationale to reduce extrapolation and demonstrate clinical relevance and translatability of the preclinical data.

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