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Systems and Network Understanding of Cancer Stem Cells

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1. Introduction

The notion that tumors arise from a rare population of cells with stem cell characteristics was first proposed more than a century ago when pathologists like Virchow and Cohnheim formulated the hypothesis that cancer results from the activation of embryonic-tissue remnants (Weiss 2000). Since then, advances in different fields have provided support to this original proposal that has led to the increasingly accepted yet controversial "cancer stem cell (CSC)" hypothesis that explains the development of multiple forms of human cancers (Wicha et al. 2006). The first experiments indicating the existence of these cells were performed in animal models in the 1970s where it was concluded that only a low percentage of transplanted murine lymphoma cells formed colonies in the spleen of recipient animals (Park et al. 1971a; Bruce and VAN DER 1963). Likewise, only a minimum number (1 in 100 to 1 in 100,000) of murine myeloma cells were able to form colonies in *in vitro* experiments. This low *in vivo* and *in vitro* clonogenic potential of tumor cells was subsequently observed for cells isolated from human solid tumors and led to the proposal that only a restricted set of cells "tumor stem cells" that have the propensity to differentiate, give rise to the entire population of cells that are present in certain tumor (Hamburger and Salmon 1977). Over the last few years, the isolation, characterization and functional analysis of CSCs have been facilitated rapid advancements in tissue culture, cell sorting, transgenic animal models and mouse-xenografting techniques (Rasheed et al. 2010). These advances have generated considerable newer insights, and thus contributed in improving our knowledge of CSCs role in cancer and have made their selective targeting a focus of central attention for cancer therapy (Toda 2009; Dodge and Lum 2011). Nevertheless, the precise origin and functional properties of CSCs remains unclear or controversial in several aspects (Hill 2006). Cancers that contain a hierarchy of epigenetically distinct populations of tumorigenic and non-tumorigenic cells might be more effectively studied and treated by focusing on the rare or cancer initiating (causing) cells (Singh et al. 2004). But this field will only achieve its promise if we carefully distinguish between cancers that follow a cancer stem cell model and those that do not (Vermeulen et al. 2008). Therapies designed to eliminate only a small subpopulation of cancer cells will likely not have a clinical impact on cancers in which tumorigenic cells represent most of the cancer cells in the patient (Huff et al. 2006; Massard et al. 2006). Additional testing of the cancer stem cell model will be required in different

cancers to determine what fraction of cases actually follow the model, and how often existing markers are informative. Such testing is likely to yield a complex picture involving differences between cancers that may vary between patients with the same cancer, in terms of the frequency of tumorigenic cells or tumor initiating cells. This is especially true for complex malignancies such as pancreatic ductal adenocarcinomas that are well recognized to be very heterogeneous in nature. Their can also be differences in the degree of hierarchical organization, and the extent to which markers can distinguish tumorigenic from non-tumorigenic cells. In this regard, the use of xenograft tumor models is considered an attractive approach for better understanding of tumorigenesis *in vivo*, the developmental relationship between cancer cells, and even new therapies. However, it is critical that such models be optimized for the engraftment of human cells if we are to draw conclusions regarding the frequency of tumorigenic cells. In this chapter, an attempt is made to revise and extend some current ideas regarding the CSC hypothesis, and how newer technologies such as systems and network biology can aid in this field.

2. Cancer stem cell *versus* clonal selection hypothesis

The fundamental concept of cancer stem cells came from early studies in leukemia and the blood forming hematopoietic stem cells (HSC). Seminal works by Till and McCulloch in the early 1960's established the existence of bone marrow HSC capable of forming myelo-erythroid colonies in the spleen of lethally irradiated hosts. These cells were later isolated by Weissman and his group where they showed that the cells were capable of self-renewal exhibiting multipotent differentiation giving rise to all the blood cell lineages (Spangrude et al. 1988). Studies in human leukemia using *in vitro* and *in vivo* colony-formation assays demonstrated that only a small subset of leukemia cells possess extensive proliferative capability, suggesting that leukemia may actually be derived from a small leukemic stem cell (LSC) population (Park et al. 1971b). This concept was further proved by the successful isolation of myeloid leukemia-initiating cells using cell surface phenotype CD34+CD38- and subsequent *in vivo* transplantation into severe combined immune-deficient (SCID) mice. Even though compelling evidence exists on the existence of stem like cancer cells, yet the hypotheses are considered controversial by purist believing in clonal evolution theory. In the following passages we will discuss the existing concepts and also demonstrate how newer technologies such integrated network and systems biology can help to understand these differences in a more comprehensive way.

2.1 Cancer stem cell hypothesis

It is well established that cancer is in essence a genetic disease that arises from sequential accumulation of mutations in oncogenes and tumor suppressor genes, leading to a malignant clone (Balmain 2001). If the CSC theory is correct, then the result of this accumulation of genetic hits is, at least, one cell with CSC features that can give rise to more CSCs and create more differentiated progeny (Buzzeo et al. 2007). At what stage in the process of malignant transformation this CSC arises, is highly disputed (Potten and Loeffler 1990). An important aspect of the CSC model is the implication that in a malignancy with a defined set of genetic alterations, cells with a different malignant potential are present. In a tumor, both differentiated cells that have lost the capacity to propagate a tumor, and cells that retain a clonogenic capacity, exist. This implies that cells showing the same genotypic alterations can show a completely different potential to initiate a tumor in mice. Here we

first present evidence that this proposed difference in malignant potential is not as striking as it has been initially envisioned. It is believed that CSCs give rise to more differentiated progeny that have lost the ability for self-renewal and the capacity to initiate the formation of a tumor (Figure 1). This would imply that remnant regulatory mechanisms are present in cancer cells that guide the differentiation process in analogy to normal cell differentiation. Indeed, there are examples of malignant cells that are transformed in nonmalignant cells by non-genetical pathways such as epigenetic effects (Kim et al. 2010; Jaenisch and Bird 2003). There is growing body of evidence showing that one of the most studied epigenetic abnormalities in cancer, abnormal gene silencing associated with gene promoter DNA hypermethylation, is linked to key aspects of chromatin regulation of gene expression which maintains the state of embryonic stem (ES)/progenitor cells. This is a timely juxtaposition since there is also a growing body of data, suggesting that cancer "stem/initiating cells", especially when they may dominate in the most aggressive forms of human tumors, have a gene expression signature reminiscent of ES cells.

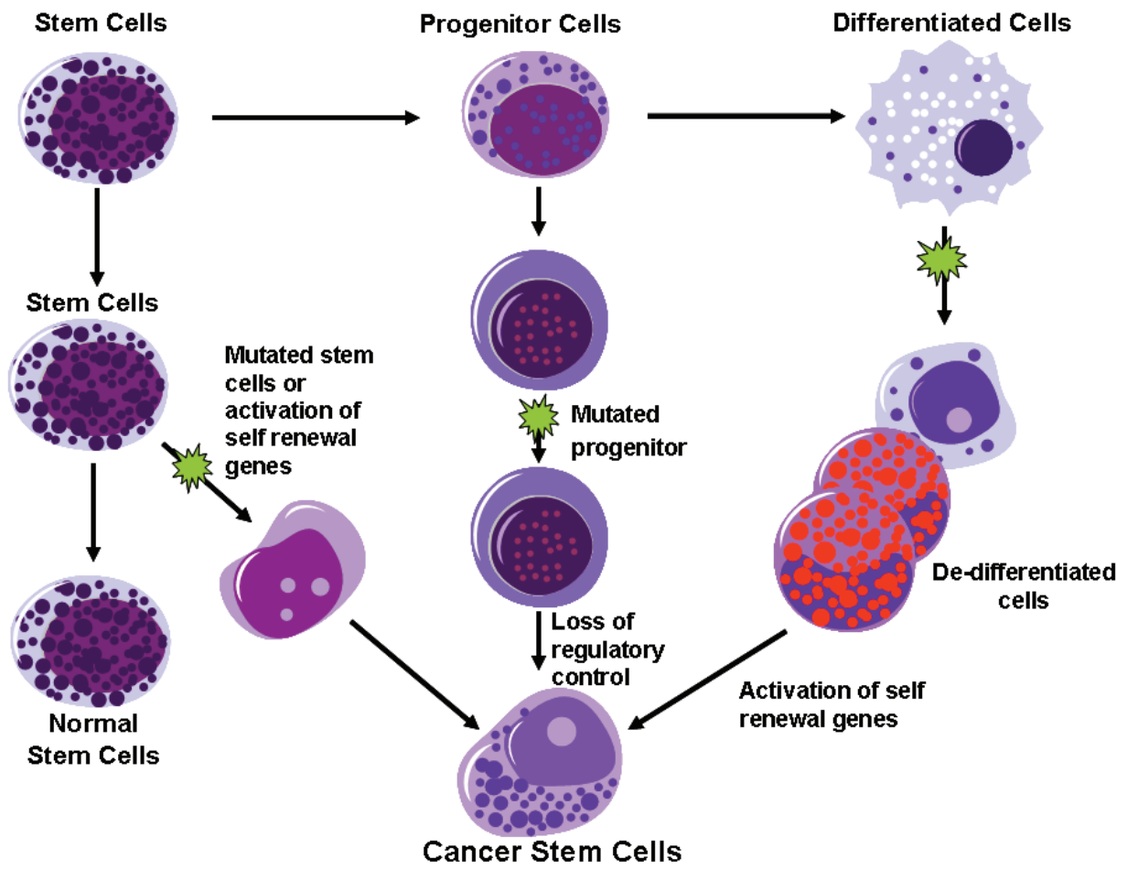

Fig. 1. Cancer stem cell hypothesis: In ideal situation normal hematopoietic stem cells give rise to progenitor cells that form differentiated cells. They can also self renew to give rise to normal cell counterparts that helps in retaining the stem cell number. However, during cancer progression multiple rounds of genetic insult/mutations in normal stem cells or progenitor cells, leads to a progressive loss of regulatory control networks that ultimately causes de-differentiation of these cells. De-differentiated cells can give rise to cancer stem cells that are different from normal progenitor or differentiated cells

Earlier studies have indicated that de-differentiated malignant cells can give rise to both malignant as well as benign cells. In these studies it was shown that mutations are not the only factors that predict the malignant potential of cells (Bissell and LaBarge 2005). Other researchers have recorded that malignant squamous cell carcinoma cells could give rise to more differentiated, non-malignant offspring (Pierce and Wallace 1971). Similarly another study, showed that subcutaneous injection of embryonal carcinoma cells can give rise to teratocarcinomas, while the same cells injected into a blastocyst developed a normal chimeric mouse (Mintz 1965; Mintz and Illmensee 1975). Refining this concept, Hochendlinger et al., demonstrated that transfer of a nucleus from a melanoma cell into an oocyte (to generate embryonic stem cells) generated chimeric mice with a normal phenotype, despite the fact that a clear increase in cancer incidence was observed (Hochedlinger et al. 2004). This work suggests that the epigenetic profile, environmental factors and proteome of the cell cytoplasm of the oocyte influences the events at the time of nuclear transfer and can compensate for mutations to a large extent. This difference in epigenetic profile could also explain the variety in tumorigenic potential of CSCs and differentiated cells in a malignancy. Indeed there is some evidence showing that epigenetic differences between CSCs and more differentiated cells exist, as there is for example, a hypermethylation described for TGFβ-RII in the mammary carcinoma non-CSCs (Shipitsin et al. 2007). Although this suggests that purely genetic models of tumor selection could go hand in hand with the CSC hypothesis, yet several crucial issues remain and can only be answered through a clonal selection perspective that is discussed in the following passages.

2.2 Clonal selection hypothesis

Proponents of clonal selection theory claim that instead of stem cell theory, the hierarchical organization of a malignancy could be easily integrated in the classical clonal selection theory of Nowell (Nowell 1971; Nowell 1976; Nowell 1989). This theory views a malignancy as a clonally-derived cell population, which acquires new potentially advantageous mutations that give rise to new more rapidly proliferating clones. This leads to a process referred to as 'tumor Darwinism', which selects for the cell type most suitable for unlimited proliferation in the given environment (Sottoriva et al. 2010) (Different cell lineages and clonal cells generations depicted in Figure 2). When one integrates the CSC theory in this model, the selection pressure is predicted to act at the level of the CSC compartment, implying that de-differentiation in CSCs results in an increase in expansion of the CSCs due to self-renewal by symmetrical divisions. This does not mean, however, that certain features present only in the more differentiated cells in the tumor could not be the subject of selection, especially if this increases the expansion rate of the CSCs from which they are derived. For example, the more differentiated cells may provide the CSC from which they are derived and which they surround a possible advantage over other clones. In this respect one could think of growth factor production, promoting angiogenesis or the production of immunosuppressive cytokines. Although this suggests that purely genetic models of tumor selection could go hand in hand with the CSC hypothesis although several other crucial issues remains to be fully elucidated.

3. Utilizing systems biology to understand cancer stems cells

Systems approaches including but not restricted to computational modeling have proven of great utility in the study of cancer, with increasing power expected to continue to emerge in the future (Wang et al. 2007). Despite notable and significant challenges that remain, three

areas that have shown significant promise is in the mining of global gene/protein expression data sets to identify molecular signatures that can be used for identification of lineage differences in cells, diagnosis of disease and treatment selection (Araujo and McElwain 2004a; Araujo and McElwain 2004b).

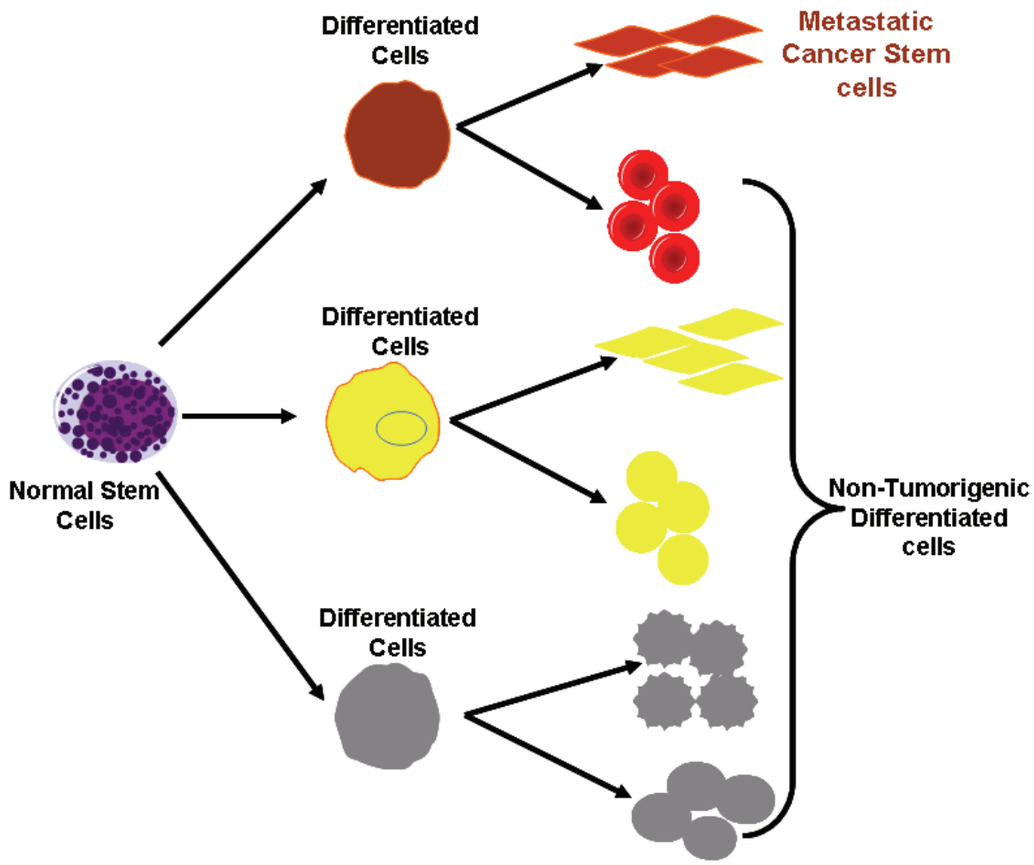

Fig. 2. Tumor clonal selection theory: Stem cells with tumor initiating capacity give rise to more differentiated nontumorigenic offspring. During the process a selection pressure is predicted to act as tumor Darwinism (here depicted by different colors) that can be beneficial for the clone yellow' or metastatic and cancerous (as shown in 'red')

As with any complex biological system, cancer (including CSCs) can be interrogated at the genome/proteome-scale using integrated systems biology approaches. Systems approaches stress three concepts regarding biological information (i) there are two fundamental types of biological information — the digital information of the genome and the environmental information that is outside our DNA. (ii) this digital genome information encodes two types of biological networks — protein interactions and gene regulatory networks. Protein networks transmit and use biological information for development, physiology and metabolism. Gene regulatory networks — transcription factors and RNAs that regulate networks of other transcription factors and other RNAs —receive information from, for example, signal-transduction networks, integrate and modulate it, and convey the processed information to networks of genes and proteins that execute developmental and physiological functions. In biological systems, these two types of networks are closely integrated. The organization of

these networks can be inferred from various different types of measurements including, for example, global measurements of dynamically changing levels of mRNAs and proteins during developmental and physiological responses, as well as large-scale measurements of protein–protein and protein–DNA interactions. (iii) the hierarchical levels of organization and information (for example, DNA, RNA and protein networks, cell signaling and metabolic networks, and organization and responses of organ systems). To understand biological systems, information must be gathered from as many information levels as possible and integrated them into models that generate testable hypotheses about how biological systems may function.

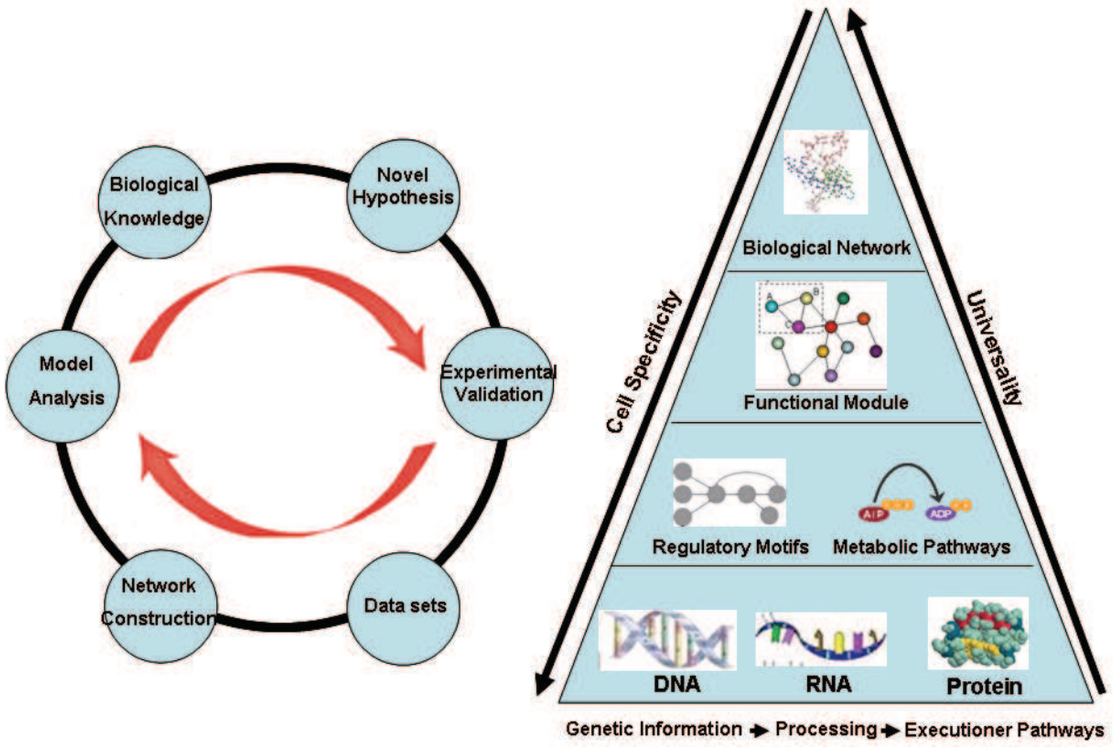

Fig. 3. Systems biology: [Left panel] complex data sets, and complex networks, can rarely be understood using intuition, or traditional biological tools. Instead, an interdisciplinary approach, involving techniques from the mathematical, integrated/computational, physical and engineering sciences is required. To be fully effective such an approach needs to repeatedly traverse an interactive cycle of collaborative interaction between biological knowledge and the proposed hypothesis that has to be validated by robust experimentation. The obtained datasets can be constructed into networks that can be correlated to the available biological knowledge and analyzed in light of the hypothesis. [Right panel] life's complexity pyramid showing hierarchy of structures from basic genomic information at the base to regulatory motifs, functional modules and large scale biological networks. The upward directed information is universal in nature while the information flow downstream of a network is cell/organism specific. Systems biology can help in understanding the inherent differences between CSCs and other cancer cell types through analyzing differences in biological networks in this complex pyramid. (Figure adapted from Oltvai ZN and Barabasi OL, (2002) Science 25, 763-764)

Following on the successes of molecular profiling in identifying prognostic signatures for many cancers, researchers have begun to perform profiling of CSCs as well (Cabanillas and Llorente 2009). Here we discuss such efforts in the context of different tumor models such as leukemia, brain, and breast. In addition to profiling for signatures of specific cancer stem cells, interesting work has also been done to find general signatures for "stemness" in tumors. For example, an 11 gene signature for "stemness" in multiple cancer types has been identified that predicts short interval to disease recurrence, distant metastasis and death from cancer (Glinsky et al. 2005). This signature/analysis reflects a BMI-1 oncogene-driven gene expression pathway, where the BMI-1 gene is essential for the self-renewal of hematopoietic and neural stem cells. Using retrospective survival analysis, this signature for "stem-ness" was found to show predictive ability in 11 different cancers, including epithelial cancers (prostate, breast, lung, ovarian, and bladder) and nonepithelial (lymphoma, mesothelioma, medulloblastoma, glioma, and acute myeloid leukemia). Thus, there is evidence that the property of "stemness" (defined with this signature) is predictive of outcome in a wide variety of tumors. If validated, it is anticipated that the observations could have a major impact on patient care. Additionally, recent studies have indicated that cancer and normal stem cells share the same self-renewal mechanisms, such as the Bmi1 and Wnt canonical pathways (Reya and Clevers 2005), further strengthening the link between stem cells and cancer stem cells. However, it is expected that normal stem cells and cancer stem cells will have certain genotypic differences, which could be further exploited for designing targeted therapy for the elimination of CSCs without affecting normal stem cells.

As mentioned earlier, tumor growth is generally accepted to be the result of several highly complex interacting processes. Fundamental cellular characteristics such as genetic and epigenetic features influence signal transduction activities that, in turn, control cellular functions. Additionally, environmental factors including nutrients and growth factor concentrations interplay with these processes. To study the emergent properties of such systems regarding proliferation speed, infiltrative growth, and phenotypical evolution of cancer, a number of advanced mathematical models have been developed (Anderson and Quaranta 2008). Using these models, some inroads have been made in understanding such hierarchical organized cancer cell populations on solid tumor growth dynamics and progression. In this study, it has been described that implementing the developing concept of CSCs in a mathematical tumor growth model directly results in an invasive morphology. Moreover, it was found that hierarchical organized malignant clones have highly altered evolutionary dynamics. Most strikingly, the CSC organization promotes phenotypical heterogeneity, a feature that could have immediate consequences for therapeutic resistance.

4. Molecular networks of cancer stem cells

Systems approaches to CSC characterization require not only the identification of the key components of a system through global analyses, but also require information about how these components interact in biological networks. Network models of multiple types have been applied to CSCs. The most commonly applied technique to CSC are interaction networks, including protein-protein interaction networks, protein-DNA interaction networks and so forth. Gene expression data can be used to identify differentially expressed genes which could then be visualized on interaction networks, as has been done for different cancers. Various properties of these networks have been studied, with reported findings including, for example, the enrichment of CSC related genes among the "hubs" of the networks. While these interaction networks are very useful tools for visualizing large data

sets, they are not computable whereas predictive network models could hold the most promise for predictive medicine and drug development. Predictive models stemming from mathematical descriptions of biochemical reaction networks and statistical influence models, where CSCs should prove highly useful and are currently being worked upon towards refinement.

Another area of network modeling that should prove very beneficial in research of cancer and CSCs is that of metabolic networks. Key metabolic differences have been shown to exist in normal stem cells vs. CSCs which have been hypothesized to be exploited using Positron Emission Tomography (PET) to do *in vivo* imaging of tumors and even to predict treatment response. If key metabolic differences can be found between CSC and the rest of the tumor, such approaches could potentially even be used to identify the location of CSC populations *in vivo*. One enabling resource for large-scale quantitative modeling of metabolic networks in cancer is the recent stoichiometric reconstruction of known human metabolism at the genome-scale (Radrich et al. 2010). With this global reconstruction, gene expression and other data can be used to create initial models of the genome-scale metabolic networks of a variety of human cell types, including cancer stem cells. These biochemical reaction networks can be useful to make numerous quantitative simulations that have been shown previously to match well with experimental data in model organisms (Wilkinson 2009). These successes with model organisms have also been extended to models of simple systems in yeast to human erythrocyte models (Duarte et al. 2007; Duarte et al. 2004b; Duarte et al. 2004a), with the global metabolic reconstruction poised to allow for larger human metabolic networks that could now be modeled. These studies may well provide insights into the unique metabolic features of cancer cells—allowing one to identify both metabolic features that are shared among cancer cells and features that are unique to individual types of cancer.

More detailed dynamic models of specific biochemical networks in cancer have been made for important signaling networks in cancer, leading to insightful biological observations that have been derived from among many others, the NF-κB signaling network (Lee and Covert 2010; Tay et al. 2010; Covert et al. 2005; Hoffmann et al. 2002; Werner et al. 2005). As isolated CSC populations become better characterized, it will be possible to model these systems to identify differences in their regulation of CSCs and further identify possible therapeutic targets. Dynamic simulations of large-scale signaling networks in cancer cells have also been performed (Christopher et al. 2004). Large amounts of high-throughput data (i.e. transcriptomes) can be used to infer networks that can explain statistical dependencies seen in the data, indicating candidate novel interacting partners, and quantitatively predict the gene expression resulting from knockouts or environmental perturbation. For model systems, such approaches are now being successfully applied at the genome-scale for gene-regulatory networks (Bonneau et al. 2006; Bonneau 2008; Hayete et al. 2007). Such approaches are now also being applied to mammalian systems as was done for normal and cancerous B-cells with the development of an algorithm called Reconstruction of Accurate Cellular Networks (ARACNe) (Basso et al. 2005; Basso and la-Favera 2007). As CSC populations are profiled extensively, these same approaches will be useful to identify predictive networks for CSCs. Comparing these networks to those in normal stem cells and other tumor cells should prove highly informative for identifying drug targets unique to the CSC population of interest. By generating networks of CSCs in particular and comparing them with networks of normal stem/progenitor cells, we should be able to greatly enhance our understanding that could lead to the characterization of cells that becomes cancerous. Computational modeling and systems approaches will be key to catalyzing the future of drug discovery (Hendriks 2010; Kumar et al. 2006; Hood and Perlmutter 2004), and thus

drug discovery focused specifically on CSCs offers tremendous promise for advancing cancer therapies. Therefore, computational modeling of CSC networks to identify potential therapeutic targets and to predict the effect of drug-induced perturbations is critical for this field moving forward.

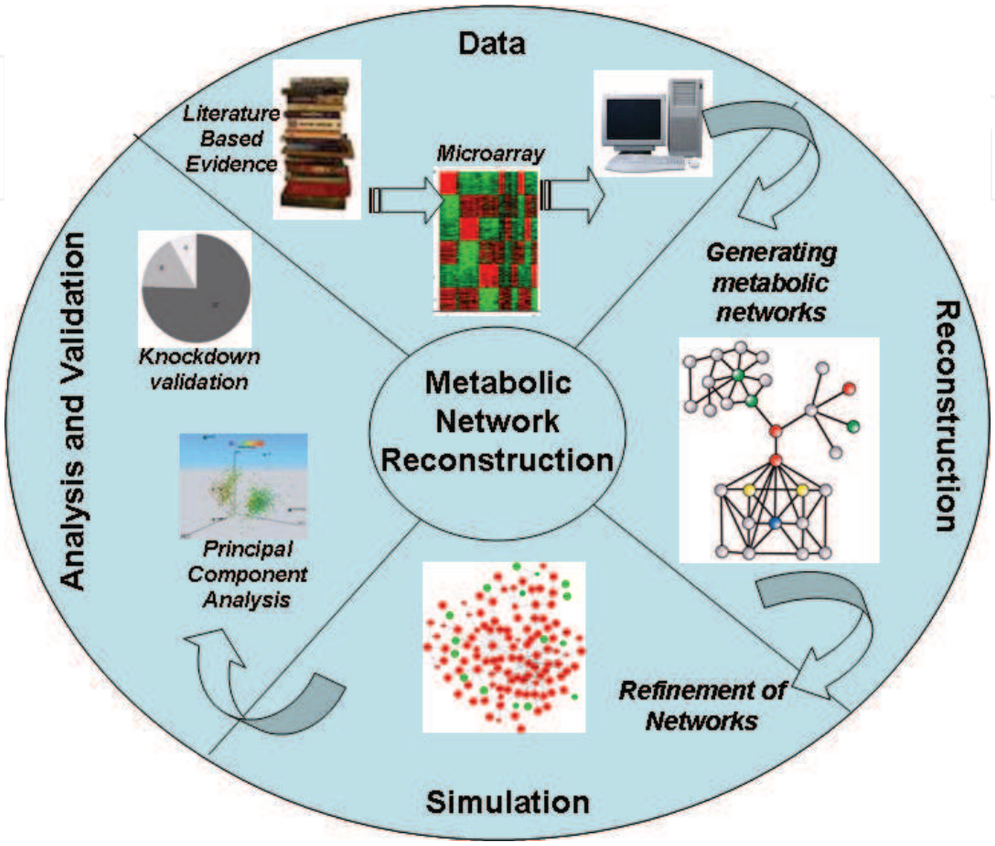

Fig. 4. Designing metabolic networks to understand CSCs: Datasets obtained from microarrays of regular cells and CSCs can be constructed to obtain complete metabolic networks. After refinement of these networks, validation can be done to differentiate key differences between these cells using molecular network silencing technologies. Finally the outcome can be correlated with literature based evidence

5. Systems understanding of CSC response to therapeutic interventions

Once the CSCs are indentified and causal link between CSC and tumor growth is established then the burning question would be how one can investigate the therapeutic intervention, tumor response and tumor relapse. It is well recognized that CSCs are more resistant to therapeutic interventions such as chemotherapy or irradiation compared with their differentiated counterparts (Jordan et al. 2006). More significantly, tumors that relapse after seemingly successful therapy are believed to regrow from the CSCs that survived the therapeutic regimen (Rich 2007; Rich and Bao 2007b). Recently, a number of studies have investigated the dynamics associated with therapeutic interventions that are either selective for CSCs or equally efficient against both cell types. It has been found that the morphology and growth kinetics of relapses for both types of therapeutic interventions are very much

different (Rich and Bao 2007a). Relapse after therapy that specifically targets non CSCs is accompanied by enhanced invasive growth patterns whereas relapsing tumors after stochastic tumor cell killing are similar to the malignancy before treatment. Simultaneously, in case CSCs are resistant to therapy, the pace at which the malignancy relapses is greatly enhanced due to the presence of relatively high fraction of CSCs directly following therapy. Also, the invasiveness of the recurrent tumors is markedly increased following intervention that is not effective against CSCs. These findings are in line with a range of clinical observations describing increased growth speed and enhanced invasion in the relapsing malignancy that are mostly attributed to the selection of more aggressive clones by the drug (Huff et al., 2006). Nevertheless, these observations could be partially explained by the failure of conventional therapies to eradicate the CSC compartment and the subsequent relapse dynamics in CSC-driven tumors. Furthermore, evaluation of evolutionary dynamics during relapse after both types of intervention reveals significant differences as well. Following therapy which is ineffective against CSCs, relapsing tumors display a marked increase in heterogeneity, whereas therapy that does target CSCs results in a dramatic decrease of heterogeneity (analyzed in article by Sottoriva et al 2010). This latter scenario is related to the fact that relapses are very much different compared with the primary malignancy with respect to the clonal lineages that contribute to the relapse of the tumor. In summary, these observations clearly indicate that applying therapy that is ineffectively targeting the CSC population is not only unsuccessful in curing the patient but would also promote malignant features including rapid expansion, increased invasion, and further stimulates heterogeneity directly after therapy. Therefore, overall understanding of the molecular expression differences and network modeling would allow for designing targeted therapy in the future for overcoming therapeutic resistance in order to eliminate tumor recurrence and metastasis.

6. Conclusion

The identification and prospective isolation of CSCs from leukemia, pancreatic and a number of other solid tumors has spawned a new paradigm in cancer research. Incremental progress has been made in understanding the critical differences between CSCs and other counterparts in the tumors, ranging from gene expression, protein expression, metabolic expression and microRNAs that are becoming emerging areas of network research. However, much needs to be learned on the differences between these cells in order to make progress towards the development of novel therapeutics that will specifically target CSCs but not the normal stem cells. Although traditional science has been helpful in understanding few differences but has been restricted to marker identification. In order to make substantial progress in characterization of these elusive cells, newer and integrated technologies are needed that take a holistic view of the cellular system in the context of tumor microenvironment. Systems biology along with molecular network modeling can be utilized with the goal of predictive, preventive, personalized, and participatory medicine for specifically targeting CSCs. This technology utilizes global assessment of cancer stem cells and their microenvironments (niche) at the level of complete transcriptome, proteome, and epigenome, using empowering new high throughput technologies. The resulting gene expression profile signatures of CSCs would serve as more accurate indicatives for cancer diagnosis and prognosis. Emerging proteomic technologies employing mass spectrometry and protein chip platforms would allow for identification of better cell-surface markers and their interaction with the resident stem cell niche, which will provide the potential

diagnostic markers from both body fluids and tumor tissues. Similar exploitation could also be done for microRNAs that are becoming important regulator of gene expression in tumors and body fluids. Although the systems biology methodologies are still developing and error prone, nevertheless, the initial version of the interactomes are of sufficient quality to provide insight into the differences between normal hematopoietic cell and CSCs. It is anticipated that incorporating these data into biological networks will provide fundament insights into the biology of CSCs and their abilities for self-renewal and differentiation. These combined efforts will ultimately lead to newer therapeutic strategy specifically by targeting CSCs for unprecedented design of personalized cancer therapy.

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Cancer Stem Cells - The Cutting Edge

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Over the last thirty years, the foremost inspiration for research on metastasis, cancer recurrence, and increased resistance to chemo- and radiotherapy has been the notion of cancer stem cells.The twenty-eight chapters assembled in Cancer Stem Cells - The Cutting Edge summarize the work of cancer researchers and oncologists at leading universities and hospitals around the world on every aspect of cancer stem cells, from theory and models to specific applications (glioma), from laboratory research on signal pathways to clinical trials of bio-therapies using a host of devices, from solutions to laboratory problems to speculation on cancersâ€™ stem cellsâ€™ evolution. Cancer stem cells may or may not be a subset of slowly dividing cancer cells that both disseminate cancers and defy oncotoxic drugs and radiation directed at rapidly dividing bulk cancer cells, but research on cancer stem cells has paid dividends for cancer prevention, detection, targeted treatment, and improved prognosis.

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