Oncolytic adenoviruses targeted to cancer stem cells

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Abstract
Cancer stem cells (CSC) represent a distinct subpopulation of cancer cells of integral importance. CSCs embody the refractory nature observed among many cancers; very competent initial tumor establishment and extremely aggressive metastatic nature. Recent discoveries indicate that CSCs embody chemo- and radioresistance and have been correlated with advanced disease and resistance to current therapies, and thus help explain the treatment resistance of many cancers. As CSCs are critical for tumor initiation, progression, persistence, and the development of metastasis, the success or failure of treatment approaches may be influenced greatly by the presence and treatment sensitivity of these cells. There also seems to be a direct link between epithelial-mesenchymal transition phenomena and CSCs. Cancer cure is predicated upon effectively targeting and eradicating the CSC population. Oncolytic viruses have undergone many developments and through multiple generations offer an effective way to specifically target and eradicate CSCs, while still maintaining the ability to affect the general tumor cell population. Conditionally replicative adenoviruses (CRAd) are one virotherapy that is especially promising. Multiple advanced targeting and infectivity enhancement schemes have been developed to allow the necessary specificity and transduction efficiency required for an effective therapy. Furthermore, these advanced generation CRAds can be armed with therapeutic transgenes to generate greater antitumor effects. Although ultimately, the rewards of targeting and eradicating CSCs will be evaluated in clinical trials, there are numerous methods for isolating primary CSCs based on surface marker expression and multiple established cell lines representative of CSCs for preliminary evaluation. [Mol Cancer Ther 2009;8(8):2096–102]

Introduction
Currently, it is estimated that one in four deaths in the United States is the result of cancer. Multiple therapy modalities have been developed with various levels of efficacy and success, as such none yet with consistently reliable cure rates for advanced disease. One promising therapy modality in development is the use of oncolytic viruses. Oncolytic viruses confer cancer specificity and antitumor efficacy through a wide variety of mechanisms of action. A number of viral species have been developed into oncolytic vectors. Despite the advances made in oncolytic viral therapies, the field awaits a true revolutionary breakthrough success, as was initially envisioned with the development of the field. The limitations in success may be due to the intrinsic biological properties of the tumor targets. Notably, a subpopulation of cancer cells that are often resistant to conventional treatment regimens and are responsible for the initiation of tumors in xenograft models have recently been discovered and characterized.

This treatment resistant subpopulation still lacks full definition but has been characterized as cancer-initiating cells or cancer stem (or stem-like) cells (CSC). This subpopulation will be referred to herein as cancer stem cells (CSCs). Such CSCs have been identified and isolated in numerous organ contexts. As with other treatment modalities, previous oncolytic virus agents have targeted the general tumor cell population and have not specifically targeted the CSC subpopulation. From the viewpoint of disease phenotype, CSCs embody the refractory nature observed among many cancers; very competent initial tumor establishment (1) and extremely aggressive metastatic nature (2). Furthermore, recent discoveries indicate that CSCs embody chemo- and radioresistance (3, 4), and have been correlated with advanced disease and resistance to current therapies (2), and thus help explain the clinical treatment resistance of these cancers. As CSCs are critical for tumor initiation, progression, persistence, and the development of metastasis, the success or failure of cancer treatment approaches may be influenced greatly by the presence and treatment sensitivity of these cells. Cancer cure is predicated upon effectively targeting and eradicating the CSC population.

The Development of Oncolytic Viruses as Anticancer Agents
The use of live viruses for the treatment of cancer dates to over a century. Specifically using adenovirus (Ad) for this
application was first published in the 1950s (5). Since these early ventures into the use of oncolytic viruses, much has been discovered about the biology of cancer and the understanding of developing efficacious antitumor therapies. Furthermore, the viruses used in these experiments were wild-type strains, whereas current vectors have been developed and refined over multiple generations of modified viruses. Ad-based vectors have been promising results in clinical translation, are well characterized for manipulation, and offer a number of advantages over other viral vectors. Ad-based vectors comprise a significant portion of oncolytic vectors in clinical trials and the majority of these Ad vectors are based on the Ad serotype 5 (Ad5), however, more recently, vectors based on other serotypes, as well as other species Ads, have been developed (6–8).

Numerous oncolytic viral agents have been translated into clinical trials, ranging from phase I to phase III trials, for a variety of malignancies (9). These trials have shown encouraging safety results, however efficacy as single agents has been limited (10). Conditionally replicative adenoviruses (CRAds) constitute a significant proportion of these trials, from which several lessons have been learned. Phase I human trials with CRAds have confirmed the overall safety of this approach; unfortunately, clinical response rates have been suboptimal with current CRAd virotherapy agents.

**Advanced Generation CRAds Circumvent Earlier Obstacles to Efficacious Targeting**

Current CRAd agents have shown modest efficacies, however, these have been limited to local (intratumoral or intraperitoneal) administration with less efficacy following intravenous administration. The decreased efficacy following intravenous administration has been presumably due to liver sequestration of intravenously injected Ad. The liver tropism of Ad is also responsible for the resultant hepatotoxicity following Ad administration and has raised safety concerns slowing the progression of some vectors to clinical translation. Recent advances in the field have provided several mechanisms to decrease Ad’s liver tropism (11), thereby allowing intravascular delivery to be a viable means of administration and decreasing some of the concerns of hepatotoxicity (12). Another limitation has been poor infectivity of target tumor cells by Ad5-based vectors secondary to the decreased expression of the Ad5 primary cellular receptor, the Coxsackie and Adenovirus Receptor (CAR), on target tumor cells. To overcome this, multiple capsid modifications have led to CAR-independent transduction to enable efficient transduction of target tumor cells. Although there has been efficacy shown in decreasing tumor size and growth with CRAd administration, these effects have not been permanent, because after a lag phase the tumor invariably begins to regrow and progress. This growth is conceivably due to the inability of these previous agents to effectively target and eradicate CSCs. A new generation of CRAds has been developed that embodies advanced targeting strategies, both transcriptional and transductional targeting, infectivity enhancement of target cells, CAR-independent transduction, and decreased liver tropism. These advanced generation CRAds have also been “armed” with therapeutic transgenes that enhance the oncolytic effect of the vector, stimulate the immune response to favor tumor eradication, or attempt to alter the tumor microenvironment in an unfavorable manner via cytokine production. However, efficacy of these new generation, “armed” CRAds will be limited if CSCs are not effectively targeted and eradicated.

**Cancer Stem Cells Represent the Key Target for Anticancer Therapies**

Historic models of cancer cell propagation have been explained by the “clonal evolution” model and the “stochastic” model. The “clonal evolution” model details that tumors arise from normal cells that mutate and generate abnormal offspring that also mutate, forming a mass of genetically varied cancer cells (13). The “stochastic” model claims that every cancer cell in a tumor can ultimately acquire a capacity for self-renewal and multilineage potency so that it can repopulate an entire tumor (14). These models of cancer complement each other and have long been regarded as the only working models of cancer organization, largely because it was only recently that it was possible to isolate very small subsets of unique cancer cell populations. Furthermore, working with unselected cancer cell populations is inexpensive, and experimental responses of the bulk of these cells can be easily used as a rationale for pharmaceutical approaches against cancer. Unfortunately, and despite an enormous effort, these approaches based on the behavior of unselected cell populations, even those termed “targeted” cancer therapies, have not yet resulted in cancer cures.

An alternative model of cancer cell propagation, the hierarchical model, has been developed that better supports the experimental observations of subpopulations of cancer cells and better explains mechanisms of treatment resistance. Emerging evidence has shown that the ability of a tumor to grow and propagate is dependent on a small subset of cells. Although the exact characteristics of the tumor cell subpopulation exhibiting treatment resistance and possessing the ability to establish tumors in animal models have yet to be fully defined, and remain the subject of debate. Given their clonal nature, cancer cells undergo processes similar to the self-renewal and differentiation of normal stem cells (14). The concept of a multipotent cancer cell may explain the histologic heterogeneity found in most tumors (15). Because of their ability to recapitulate the tumor, this subset of cells has been labeled as CSCs. CSCs, which were first identified in 1994 (16), are a subset of cancer cells that are characterized by three key properties that they share with normal tissue stem cells (17). (1) They possess the ability of indefinite self-renewal (immortality); (2) They proliferate extensively and thus are selectively endowed with a tumorigenic capacity as opposed to other cancer cell subsets; and (3) they have the capability to differentiate into multiple lineages within normal tissue or tumors to sustain growth of heterogeneous cancer tissues. The existence of CSCs is further supported by the distinctive
repertoire of surface markers they express, which allow their reproducible and differential purification. Although there is still some debate if solid tumor CSCs really fit the conventional criteria of stem cells, there is accumulating evidence supporting a major contribution of this cell population to the pathogenesis and progression of many solid tumors. CSCs have been found in various types of cancers such as human leukemia (16, 18), breast cancer (19, 20), squamous head and neck cancers (21), melanoma (22), gastrointestinal cancers (23–25), prostate cancer (26), glial tumors (27), ovarian cancer (28, 29), and pancreatic cancer (1, 2).

**Cancer Stem Cells and Epithelial-Mesenchymal Transition Link**

It is still uncertain if the origins of CSCs are the result of mutations to normal tissue stem cells, from a reversible epithelial-mesenchymal transition (EMT), or another source. EMT is a common phenomena seen in many tumor subtypes that results in increased motility and invasiveness and is believed to be critical for the advancement of the tumor and the development of metastasis (30). Tumor cells that have undergone EMT exhibit many stem cell properties and conversely, many CSCs are rich in the expression of genes involved in EMT and express multiple markers associated with EMT (30, 31). Recently, a direct link between EMT and the gain of epithelial CSC properties has been proposed in the breast cancer context during cancer invasion and metastasis (31). The unusual combination of EMT with stem cell competence may define a CSC subtype that is migratory and initiates tumor invasion and metastasis (4, 32). The relationship of CSCs and the EMT phenomena seems to be critical for tumor progression, metastasis, and treatment resistance (33).

**Cancer Stem Cell Markers**

There are several cellular pathways and protein markers that are hallmarks of stem cells and have been recently described and attributed to the CSC population. For solid tumors, the repertoire of cell surface markers currently used to identify human CSCs includes CD44, CD133, epithelial surface antigen (ESA), and CD24, either singly or in combination, however, uniform definitions remain elusive (Table 1; ref. 34). One of the common markers found on most of the CSCs identified to date, including glioblastoma, hepatocellular, colon, prostate, and pancreatic cancers, is CD133 (35, 36). CD133 is a highly conserved antigen that is the human homolog of mouse Prominin-1 and a five-transmembrane domain cell surface glycoprotein expressed by untransformed hematopoietic and neural progenitor cells. In pancreatic cancer, the expression of CD133 significantly correlated with multiple clinicopathological factors, including histological type, lymphatic invasion, and lymph node metastasis. Furthermore, expression of CD133 in healthy pancreatic tissue was a very rare event (2). Consequently, the 5-year survival rate of CD133+ patients was significantly lower than CD133− patients, and the expression of CD133 was an independent prognostic factor (37). Of considerable interest is the fact that these CD133+ cells are particularly resistant to traditional chemotherapy agents and express a variety of multdrug resistance proteins (38). In melanoma and breast cancer, the CSC-like population seems to express CD44 variant isoforms with the phenotype CD44+CD24−/low cell population, rather than a CD133+ population (19, 39). Pancreatic and breast cancer initiator cells also positively express ESA, and this ESA+ phenotype may represent the CSC population in these tumors. Further, there are some solid tumor types for which the debate remains for the “true” CSC population, because multiple CSC-like subpopulations have been purified by different groups with different repertoires of cell-surface protein expression profiles. Additionally, CD24 is positively correlated with tumorigenicity in pancreatic cancer (1), but negatively correlated in breast cancer (19), yet CD24+ cells are associated with invasive breast cancer (40).

There are several highly expressed proteins and other relevant markers characteristic of CSCs. OCT4 is a gene and/or protein that plays a role in the maintenance of viability of the mammalian germ line, functioning as a stem cell survival factor, and in the induction of pluripotency in somatic cells (41). Aldehyde dehydrogenase (ALDH; ref. 42) is a detoxifying enzyme responsible for the oxidation of intracellular aldehydes and is thought to play a role in stem cell differentiation through metabolism of retinal to retinoic acid (43). β-Catenin is an essential component of both intracellular junctions and the canonical WNT signaling pathway, which has been implicated in stem cell survival (44). Overexpression of β-catenin leads to self-renewal of stem cells in vitro and in vivo and has been linked with stem cell survival and tumorigenesis (45). Furthermore, expression of β1-integrins might be a stem cell marker in several tissues, including epidermis, testis, and colonic crypts. Stromal cell-derived factor 1 (SDF-1) is a key mediator in cell migration and the expression of its receptor, CXCR4, has been strongly correlated in CSCs at the invasive front (2). Other prominent markers include musashi-1, hairy and enhancer of split homolog-1 (Hes-1), EpCAM, Claudin-7, Lgr5, Hedgehog, bone morphogenetic protein, Notch, and Wnt (4). Although markers are useful to identify, isolate, and characterize cancer cell subpopulations, there is a possible inaccuracy due to antigenic plasticity, and therefore studies based on functional assays are likely to be more reliable to identify CSCs (46). These proteins and markers offer multiple targets for the design of therapeutics to exploit.

**Cancer Stem Cells Are Critical for Metastatic Disease Spread**

In addition to tumor initiation, CSCs may be associated with cancer invasion and distant tumor cell dissemination. Gene expression profiling of CD44+ and CD44high/CD24−/low breast CSCs, compared with that in normal breast epithelial cells, identified invasive gene expression signatures that were significantly associated with both overall and metastasis-free survival (47). These signatures included numerous genes involved in cell motility, invasion, apoptosis, and remodeling of the extracellular matrix, and display activity in TGF-β signaling pathways (48). As CSCs are the predominate cell type capable of tumor initiation, then CSCs are likely the predominant cells capable of colonizing secondary organs and spawning heterogeneous metastases similar to...
the primary tumor. Studies of colon cancer progression revealed that tumor cells at the tumor-host interface (i.e., the invasive front) express EMT-associated genes as well as stemness-associated genes (48). This concept was further supported by the identification of a distinct subpopulation of highly migratory CD133+ pancreatic CSCs coexpressing CXCR4 at the invasive front of pancreatic tumors. Patients with tumors containing higher numbers of CD133+/CXCR4 at the invasive front of pancreatic tumors. Patients with tumors containing higher numbers of CD133+/CXCR4 + cells had an increased incidence of metastatic disease (2).

**Cancer Stem Cell Resistance to Current Therapies Limits Efficacy**

The existence of CSCs has profound implication for cancer biology and therapy. It has been proposed that CSCs may be particularly resistant to chemotherapy and radiation therapy (50). Many investigators now believe that many tumor cell relapses following cytoreductive treatments may be due to the inherent resistance and subsequent outgrowth of CSC clones (51). These cells are resistant to many standard chemotherapeutics because of their relatively quiescent state; thereby rendering cell cycle-dependent chemotherapeutics ineffectives. CSCs typically overexpress cell membrane drug transporters of the ATP-binding cassette system has been used in many cancer gene therapy approaches because of its high in vivo transduction efficiency. Also, the Ad is important because CSCs are generally the lowest replicating cancer cell population in the tumor (60). Also, the Ad system has been used in many cancer gene therapy approaches because of its high in vivo transduction efficiency. There is a large variety of targeting strategies available with Ad vectors. Because this virus does not have a lipid envelope, it is possible to target the viral binding and/or transduction by incorporating binding motif into viral capsids (61). Furthermore the Ad system is versatile for achieving specific replication by placing viral genes necessary for replication (Ad E1a) under control of tumor-specific promoters, thereby generating CRAds. The mechanism of cell death, “oncolysis,” by these vectors is a novel mechanism of action (MOA), which is effective against apoptosis-resistant cells. Progeny viruses can then infect adjacent cancer cells and the cycle of oncolysis can repeat itself throughout the tumor. In addition to this primary MOA, oncolytic viruses have additional complementary secondary MOAs such as induction of tumor-specific cytotoxic T-lymphocytes, tumor vascular shutdown, and chemosensitization. Furthermore, the next generation of oncolytic viruses may have additional MOAs via therapeutic transgene “arming.” These therapeutic

#### Table 1. Identified cancer stem cells and phenotypes

<table>
<thead>
<tr>
<th>Tissue and/or Cancer</th>
<th>Phenotype and/or Surface Expression</th>
<th>Other Relevant Marker Expression</th>
<th>Identifying Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia (acute myelogenous leukemia)</td>
<td>CD34+/CD38−/CD90−</td>
<td>Lin−, ESA+,CD133+</td>
<td>Lapidot et al. (16); Bonnet et al. (18)</td>
</tr>
<tr>
<td>Breast</td>
<td>CD44+/CD24+/low/Lin−</td>
<td>BMII1 (nuclear)</td>
<td>Al-Hajj et al. (19); Wright et al. (20)</td>
</tr>
<tr>
<td>Squamous cell cancer of head and neck</td>
<td>CD44+/Lin−</td>
<td>CD133−</td>
<td>Prince et al. (21)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>ABCB5+</td>
<td>CD133−</td>
<td>Schatton et al. (22)</td>
</tr>
<tr>
<td>Colon</td>
<td>CD133+</td>
<td>ALDH+</td>
<td>Haraguchi et al. (23); O’Brien et al. (24)</td>
</tr>
<tr>
<td>Liver hepatocellular cancer</td>
<td>CD44+/α2j3/+/CD133+</td>
<td></td>
<td>Ma et al. (25)</td>
</tr>
<tr>
<td>Prostate</td>
<td>CD133+</td>
<td>CD133+</td>
<td>Collins et al. (26)</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>CD44+/CD24+/ESA+</td>
<td>CD133+</td>
<td>Singh et al. (27)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>CD44+/CD24+/ESA+</td>
<td>Verapamil sensitive, CD44+, CD117+ (c-kit)</td>
<td>Li et al. (1); Herrmann et al. (2)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>BCRP1+; CD44+/CD133+</td>
<td></td>
<td>Szotek et al. (28); Zhang et al. (75)</td>
</tr>
</tbody>
</table>
payloads are expressed selectively in cancer cells during replication, resulting in complementary MOAs (62). One target of these therapeutic transgenes is the EMT phenomenon. EMT can be triggered in a context-specific manner by various extracellular stimuli. Many secreted molecules, such as Hedgehog, epidermal growth factor, hepatocyte growth factor, and members of the transforming growth factor (TGF)-β, Wnt, fibroblast growth factor, and insulin-like growth factor families, are capable of inducing EMT (63). Therefore, incorporating transgenes into the CRAd that directly counteract one or multiples of these pathways may enhance the CRAds antitumor efficacy.

Efficiently targeting Ad vectors to CSCs will likely require infectivity enhancement. CAR expression on CSCs has not been characterized for all organ types; however, on the basis of the highly variable and often decreased expression of CAR on many cancer cell types (64) and on stem cells, it is reasonable to conclude that efficient Ad transduction will require an alternate pathway. Several infectivity enhancement strategies have been developed to overcome the paucity in CAR expression and some of them have been directly applied to CSC transduction. Incorporation of an infectivity enhancement strategy in the oncolytic virus context requires genetic modification such that the progeny vectors will continue to possess the enhanced infectivity, thereby decreasing the role of adapter proteins to retarget the virus. One of the least complex methods for altering Ad transduction is substitution of the Ad fiber protein, or at least the receptor binding knob domain portion of the fiber protein, with that of another serotype (pseudotyping), or simply constructing the vector on an alternate serotype. To this end, pseudotyped Ad5 vectors have been constructed expressing knob domains from almost all of the human Ad subspecies (65, 66), as well as Ad from other host species (6), with varying levels of infectivity augmentation in cancer cells (64). Modifiable Ad vectors fully based on alternate serotypes and other host species have also been constructed (7, 8). Another means of altering the transduction of Ad vectors is with the insertion of receptor binding peptides into the fiber protein (61), or other capsid proteins (67). These various strategies can be used independently or in combination to acquire the desired levels of transduction of the target cell population (68, 69). In relation to CSC transduction, several of these strategies have been investigated with multiple vectors, notably pseudotyped vectors with Ad3, Ad16, and chimpanzee Ad serotype 23, demonstrating effective transduction of breast (70) and brain (71) CSCs.

Current Efforts for Using Oncolytic Viruses to Target Cancer Stem Cells

A few groups have begun developing oncolytic Ads targeted to CSCs in the context of neuroblastomas, esophageal cancer, and breast cancer. Zhang and colleagues engineered a telomerase-specific oncolytic Ad vector carrying the apoptotic tumor necrosis factor-related apoptosis-inducing ligand and E1A gene. This vector showed preferential targeting to radiosensitive esophageal CSC-like cells (71). The human telomerase reverse transcriptase promoter (hTERT) is an attractive CSC target due to the requirement of telomerase activity in CSCs and the overexpression of telomerase in many cancer types. Expression of putative stem cell markers β-catenin, Oct3/4, and β1-integrin were also significantly increased in these radioreistant esophageal cancer stem-like cells (72). Eriksson and colleagues have constructed various infectivity enhanced oncolytic Ads that have shown favorable results against breast CSCs. Capsid-modified adenoviral vectors were effective in killing CD44⁺CD24⁻/low cells in vitro and in vivo. Furthermore, the same group has characterized various promoters; including cyclooxygenase-2, multidrug resistance, telomerase (hTERT), and α-lactoalbumin, which are all active in breast CSCs that have been incorporated into an oncolytic Ad-targeting strategy demonstrating complete eradication of CD44⁺CD24⁻/low breast CSCs in vitro and a significant antitumor effect in vivo (73). These vectors were also based on an Ad-pseudotyped infectivity enhancement strategy to allow efficient transduction of CSCs in a CAR-independent fashion. Mahler and colleagues exploited a transcriptionally targeted herpes simplex virus (HSV)-based oncolytic vector to target neuroblastoma CSCs. The oncolytic HSV vector had expression of the HSV-1 neurovirulence gene driven by the nestin enhancer and showed efficient cell killing of the CSCs as well as the general neuroblastoma population (46). Although this group didn’t use an Ad-based vector for these experiments, similar targeting strategies have been done with CRAds targeted to general tumor populations.

Cancer Stem Cell Models

The CSC subpopulation is a minor component of the tumor cell population in number but plays perhaps the largest role in tumor progression. Devising treatments to target this population and to effectively test them will rely on harvesting and isolating primary CSCs from patients; however this can be an expensive, difficult, and meticulous process resulting in low yields of cells. Although final testing of a treatment agent may require primary CSCs from human patients, preliminary studies may be done using selection techniques and cell lines that mimic CSC populations rather than the general cell line population. CSCs may be purified from primary human tissues or established cell lines via a variety of methods including Hoechst dye efflux, suspension sphere assays, serial transplantation, and differential cell-surface protein expression. Not all established cell lines contain CSC-like subpopulations. An investigation for the presence of CSC subpopulations in 33 breast cancer cell lines, found only 23 of the 33 displayed stem cell properties in vitro and in NOD-SCID xenografts; however, these cell line subpopulations did reflect CSC properties and had significant metastatic potential (74). Furthermore, an independent group found 7 of these 23 breast cancer cell lines had a CD44⁺/CD24⁻/ESA⁺ subpopulation that could self-renew, reconstitute the parental cell line, could retain 5-Bromo-2-deoxyuridine (BrdU) label, an assay that illustrates slower cell cycle kinetics and likelihood of chemotherapeutic resistance, and as few as 100 of these CSC-like cells were tumorigenic in NOD-SCID mice (75). Similar studies of neuroblastoma (46) and pancreatic cancer cell lines have isolated cell lines...
containing subpopulations that could be purified by fluo-
rescence-activated cell sorting (FACS) for stem cell markers
such as CD133 or by incubating the cell lines in the pres-
ence of chemotherapeutic agents and selecting for resistant
populations. These studies all support the notion that sub-
populations from established cancer cell lines could be
used to test new treatment strategies; however, these stud-
ies should be preliminary to further studies with primary
human tumor material and purified primary CSCs.

Conclusion
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tion of tumor metastases, CSCs are integral targets for novel
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