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Immunity to stemness genes in human cancer

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Abstract

A growing body of data points to intraclonal heterogeneity and hierarchy of growth potential, but also plasticity of cellular differentiation within human tumors. Recent studies have also identified surprising overlap between pathways that regulate pluripotency in embryonal stem (ES) cells and oncogenesis. While there is a long history of targeting embryonal tissues towards cancer vaccines, recent identification of critical stemness pathways in ES cells, as well as putative cancer stem cells (CSCs) provides novel opportunities for antigen-specific targeted therapy. Here we discuss recent insights into the capacity of the immune system to target these pathways. Immunologic targeting of pathways associated with stemness has implications for both immune regulation of tumor growth as well as regenerative therapies with embryonal stem cells.

Cancer cells share several properties with stem cells including the capacity for long term persistence and self renewal[1,2] Pathways that regulate the biology of stem cells have striking overlap with critical checkpoints that regulate the growth of cancer cells[3-5]. In this review, we discuss recent insights into the capacity of the immune system to target these pathways and argue that such pathways are potentially important targets for the capacity of the immune system to control cancer. The ability to harness the properties of these immune responses also has implications for the emerging field of regenerative medicine targeting embryonal stem (ES) cells.

Pluripotency, Stem Cells and Cancer

A major insight in developmental biology has been the recent demonstration that a limited set of genes are sufficient to induce pluripotency in adult differentiated cells[6,7] ••. However these studies also indicate that induction of pluripotency is intricately linked to cancer. Indeed formation of tumors is used as one of the criteria for evaluating the induction of stemness itself and tumorigenicity of stem cells in regenerative medicine is directly proportional to their pluripotency (Figure 1). Interestingly, genes such as p53 which regulate oncogene-mediated induction of cancer also regulate the formation of such induced pluripotency stem (iPS) cells [3,4,8,9]. The presence of embryonal stem cell like gene expression programs is detected in several human cancers and correlate with adverse outcome[10-12] ••. Expression of these genes also correlates with subtypes of cancers typically associated with aggressive clinical course, such as those with undifferentiated histology[11]. At least a proportion of these programs may be directly activated by oncogenes such as Myc, implicated in several human tumors[13]. Recently, more direct evidence linking pluripotency genes to cancers has also emerged. For example, aberrant expression of OCT4 is sufficient to induce tumors in mice[14]. SOX2 was

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recently identified as a common target of genomic amplification and a lineage survival oncogene in patients with lung cancer[15]. Myc is already a well recognized oncogene. Together these data suggest that inappropriate expression of stem cell programs may be a hallmark of both murine and human tumors, and perhaps its Achilles heel.

Pioneering studies in leukemia, later extended to solid tumors have suggested the presence of intraclonal hierarchy with subpopulation of tumor cells enriched for clonogenic growth, termed cancer stem cells (CSCs)[16,17] ••. These cells have typically been defined on the basis of their ability to seed tumors in animal hosts, to self renew and to spawn differentiated progeny. Several groups have documented the enrichment of ES associated genes in CSCs, suggesting that these cells may utilize similar programs for self renewal[2]. Part of the controversy regarding CSCs results from differences in frequencies of these cells depending on the specific model used[18,19]. Indeed, recent studies suggest that the CSC like properties may be a function of the cell type of origin, stromal microenvironment, accumulated somatic mutations and the stage of malignant progression. The CSC model therefore needs to be interpreted in light of evidence regarding the plasticity of the differentiation status of tumor cells. Thus, interactions of tumor cells with their microenvironment can lead to altered differentiation, termed epithelial-mesenchymal transition (EMT) in the case of solid tumors[20]. Such dedifferentiation can also be seen experimentally in hematopoietic tumors with a differentiated cell phenotype, such as myeloma, particularly in the context of signals from the microenvironment [21]. Experimental data suggest a strong overlap between EMT and stem cell phenotype in cancer[20]. The phenotypic plasticity of tumor cells also suggests that a dynamic equilibrium may exist between CSCs and non-CSCs, depending on signals from the microenvironment[22] •. We suggest that a critical target from the perspective of tumor immunity may not be a particular cell type (which may be a moving target), but the property of stemness itself.

Immune targeting of stemness- pros / cons

Sequencing of the cancer genomes has illustrated the plethora of mutations that exist in each tumor, some of which drive the oncogenic process[23]. These may, in principle, represent attractive targets for tumor immunity[24]. Other classes of targets include non-mutated differentially expressed antigens, as well as proteins (such as cancer-testis antigens) aberrantly expressed as a result of epigenetic alterations in tumor cells. While a case can be made for each of these classes of antigens, which, if any of these antigens might serve as a true tumor rejection antigens in the clinic remains unknown[25]. We argue that one size fits all may not apply for immune therapy of cancer and that optimal targets for tumor immunity may depend on the underlying genetic lesions within tumors, and the biology of the resulting tumors. In this regard, tumor types most dependent on CSCs for their growth kinetics may be the best suited for approaches targeting stem cell genes. The concept that CSCs and non-CSCs may exist in a dynamic equilibrium also argues for a need to target CSCs, or genes associated with stemness. One prediction from this concept is that unless CSCs are effectively targeted, tumor immunity might paradoxically lead to enrichment of less differentiated cells, such as those with EMT. Such an observation has indeed been made in some experimental murine models[22]. However whether this happens clinically remains to be shown. Targeting only the more differentiated or transit amplifying compartment may also set up a vicious cycle of homeostatic regeneration, analogous to chronic wounds. Such a process has been implicated in the setting of autoimmune myopathies, but may also have a parallel in cancer immunity[26].

Immune targeting of stem cell genes also carries potential risks. The most obvious risk relates to pathways shared with normal adult stem cells. In this setting, autoimmunity would carry substantial risk of toxicity to normal stem cells. Immune tolerance to pathways shared between CSCs and adult stem cells also represent a potentially formidable challenge. We suggest that

the group of genes most attractive as immune targets in this setting are genes expressed in or shared between cancer (or CSCs), and embryonal stem cells (ESCs), but not adult stem cells or their progeny (Figure 2). T cells against such targets may also be less susceptible to tolerance mechanisms to prevent autoreactivity to normal tissues or stem cells. In this regard, it is of interest that at least some of the ESC associated genes expressed in putative CSCs appear to be dispensable for the function of adult stem cells. One example is the pluripotency gene OCT4, which has been shown to be oncogenic in vivo, but is dispensable for the function of adult stem cells[14,27]. However at this time, the capacity of the human immune system to target such genes is not well understood.

Immune responses to ES associated genes in cancer

Attempts to vaccinate against cancer using embryonic material has a long history of over 100 years in cancer immunology (reviewed recently by Brewer et al)[28]. Much of these early attempts preceded any biologic understanding of the properties of stem cells. Interestingly, even in these studies, the protective effects of vaccination were limited predominantly to early stage, but not later stage embryos, which led to much confusion. Nonetheless, investigations in this field led to the discovery of several oncofetal antigens, such as carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), and prostate specific antigen (PSA), which continue to have clinical utility to date and serve as important targets for cancer therapy, including vaccines. It is however only recently that we have a much better appreciation of the stemness programs that regulate different stages of development. For example, recent studies have shown that the a limited set of core transcriptional factors, namely SOX2, OCT3/4 and Nanog regulate the stemness and pluripotency of ES cells[29]. These insights provide novel opportunities to explore immune recognition of these antigens or pathways.

Evidence supporting the ability of the human immune system to mediate T cell responses against ES associated stemness genes came initially from antigen discovery approaches applied to cohorts of patients with clinical cancer or premalignant states. Multiple myeloma is a plasma cell tumor preceded by common premalignant state, monoclonal gammopathy of undetermined significance (MGUS). Analysis of host response against a panel of tumor antigens suggested that targets of host response in MGUS differed from those in myeloma. Interestingly, the top gene differentially targeted by the immune system in MGUS was the pluripotency gene, SOX2 [30] ••. The presence of naturally occurring T cell responses against SOX2 in MGUS patients was predictive of an indolent course and markedly reduced likelihood of progression to clinical myeloma requiring chemotherapy. Expression of SOX2 correlated with the putative clonogenic compartment in MGUS, and SOX2 specific T cells inhibited the clonogenic growth of MGUS cells in culture. Antibodies against SOX2 have also been observed in patients with lung cancer, wherein they correlate with improved outcome, although cellular immunity to this antigen in patients with lung cancer has not yet been examined[31] ••. Antibodies to SOX2 are also detected in patients with meningioma, a benign tumor with an indolent course in most patients [32]. Other investigators have recently made similar observations when comparing targets of immune response in preneoplastic to malignant lesions. For example, immunity to another developmental antigen OFD1 was detected in MGUS, but not in myeloma[33]. OFD1 is also implicated in morphogenesis, although its role in carcinogenesis is not presently clear. Together these studies suggest the possibility that the nature of specific targets of spontaneous immunity may be predictive of clinical outcome in patents with cancer or more importantly, in otherwise healthy individuals or those with preneoplastic states.

Two other genes relevant to the biology of ES cells and targets of anti-tumor immune response are the tumor suppressor gene p53 and telomerase reverse transcriptase (TERT). However in contrast to the pluripotency genes discussed above, these genes are also expressed in and are important for the function of nonmalignant cells, as well as adult stem cells. Preclinical studies

described anti-tumor efficacy of immunity against p53[34,35]. Both humoral and cellular responses against p53 can be detected in patients with cancer, and early phase studies to harness these responses are ongoing[34,35]. Similarly, both naturally occurring and vaccine induced T cell responses against hTERT can be elicited in patients with cancer[36]. However, whether T cells against these antigens can mediate the rejection of human tumors remains to be established. As the expression of these genes is not restricted to tumor cells, potential toxicity in terms of reactivity to normal tissues is also a potential concern. Another class of genes, cancer-testis antigens represent genes expressed predominantly in germ cells and a subpopulation of tumor cells, but not in normal tissues[37]. The expression of these genes is linked to the altered methylation status of the cancer genome and often correlates with adverse outcome of tumors. These genes were among the first defined human tumor antigens and have been extensively studied, particularly as the lack of expression in normal tissues makes them attractive targets for vaccines. It has been argued that the subpopulation of tumor cells expressing cancer-testis antigens may be enriched in CSCs [38], however the functional significance of C/T antigens in cancer is still largely unknown. The emerging data discussed above suggests that the immune system surprisingly lacks tolerance to antigens expressed on ES cells. It is of interest to ask whether there is a much broader repertoire of ES associated genes to which the human immune system can potentially respond. It would be important to better understand the properties of this immune response, and the mechanistic basis for the apparent lack of immune tolerance to this set of genes. The capacity of the immune system to target stem cell associated genes is particularly relevant for two emerging clinical areas, targeting putative CSCs; and ES / iPS derived regenerative medicine, as discussed below.

Immune targeting of cancer stem cells

CSCs have been shown to be intrinsically resistant to traditional chemotherapies and implicated in disease recurrence[1]. This has prompted exploration of alternate approaches. Recent data suggest that immune based approaches may be particularly attractive towards targeting CSCs. One strategy is to target CSCs via monoclonal antibodies targeting antigens differentially overexpressed on these cells. Two recent examples of such an approach are antibodies targeting CD123 and CD47, which have been shown to eradicate leukemia stem cells in preclinical models[39,40] ••. It is likely that in the coming years, several other targets overexpressed on putative CSCs will be found, which may provide novel opportunities for targeting these cells.

Another approach involves harnessing cellular immune responses against these cells. Such an approach was tested in the context of minor histocompatibility antigen reactive T cells against leukemia stem cells[41,42]. T cells against a Y chromosome encoded antigen, DDX3Y, were identified in the context of a patient in clinical remission following sex mismatched allogeneic stem cell transplant, and shown to target leukemia stem cells[43]. Anti-tumor T cells in MGUS, particularly those reactive against ES antigen SOX2 can inhibit the clonogenic growth of tumor cells. Indeed, the expression of SOX2 was shown to be enriched in CD138- subpopulation of tumor cells, thought to be enriched in the clonogenic potential in MGUS[30]. Other investigators have also shown the capacity of T cells to inhibit the clonogenic growth of MGUS cells in culture[44]. Data regarding targeting CSCs via anti-tumor T cells has also emerged from solid tumors[45,46]. T cell immunity against SOX2 and SOX6 has been explored in the context of glioma stem cells[47,48]. Dendritic cell (DC) mediated targeting of neurospheres known to be enriched in CSCs led to greater anti-tumor immunity in mice compared to targeting bulk tumor cells[49]. In another preclinical 9L glioma CSC model, DCs loaded with glioma CSCs, but not daughter cells or conventionally cultured 9L cells prolonged survival in animals bearing 9L CSC tumors. CSCs in human glioma are thought to be enriched in CD133+ subpopulation[50]. Brown et al demonstrated the capacity of cytomegalovirus (CMV) pp65 specific T cells to kill pp65 expressing glioma CSCs, supporting the capacity of T cells to target these cells[51]. Even injection of bulk ES or iPS cells has been explored and shown to induce

protective immunity in a colon cancer model[52]. Clearly, better understanding of antigenic targets on CSCs in different tumors is needed to further explore immune targeting of CSCs in the clinic. However, the emerging data do point to the feasibility of immune based targeting of CSCs and suggest that exploring new strategies to harness immunity to these cells or pathways are worthwhile.

Stem cell tumorigenicity and safety of regenerative medicine

Recent discovery of induction of pluripotency by a core set of factors has led to the promise of regenerative medicine using such cells[7]. However such induced pluripotent stem cells are predicted to possess tumorigenic potential equal to or greater than ES cells[53]. The nature of tumors associated with ES or iPS therapy is not restricted to teratomas but includes diverse tumor types[54,55]. Indeed, all four of the core IPS factors are now strongly implicated in cancer, as discussed earlier. The tumorigenic potential of ES or iPS cells seems to be related to their differentiation status[56]. Therefore, one approach being taken to reduce risk of tumors with stem cell based therapy is not to inject the stem cells themselves, but their differentiated progeny. However this approach may reduce the very promise of stem cell therapy and still carries considerable risk, as differentiation is a dynamic process, not an on-off switch. Recent findings that the immune system has the capacity to target ES pluripotency genes [30]suggest the possibility that harnessing such an immune response may allow reduction of tumorigenicity of iPS based regenerative therapy.

Conclusions

Recent insights in stem cell biology have major implications for understanding the development of cancer, as well as harnessing immune response against cancer. In this review, we have tried to argue that pathways or genes that regulate stemness in embryonal or cancer cells may be critical targets for cancer therapy and that these may be targeted via the immune system. The capacity of the immune system to target these genes also has implications for preventing tumors during stem cell based therapies.

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Abbreviations

ES	embryonal stem cells
iPS	Induced pluripotency stem cells
CSC	cancer stem cells
EMT	epithelial-mesenchymal transition
MGUS	monoclonal gammopathy of undetermined significance
TERT	telomerase reverse transcriptase

DC	dendritic cells

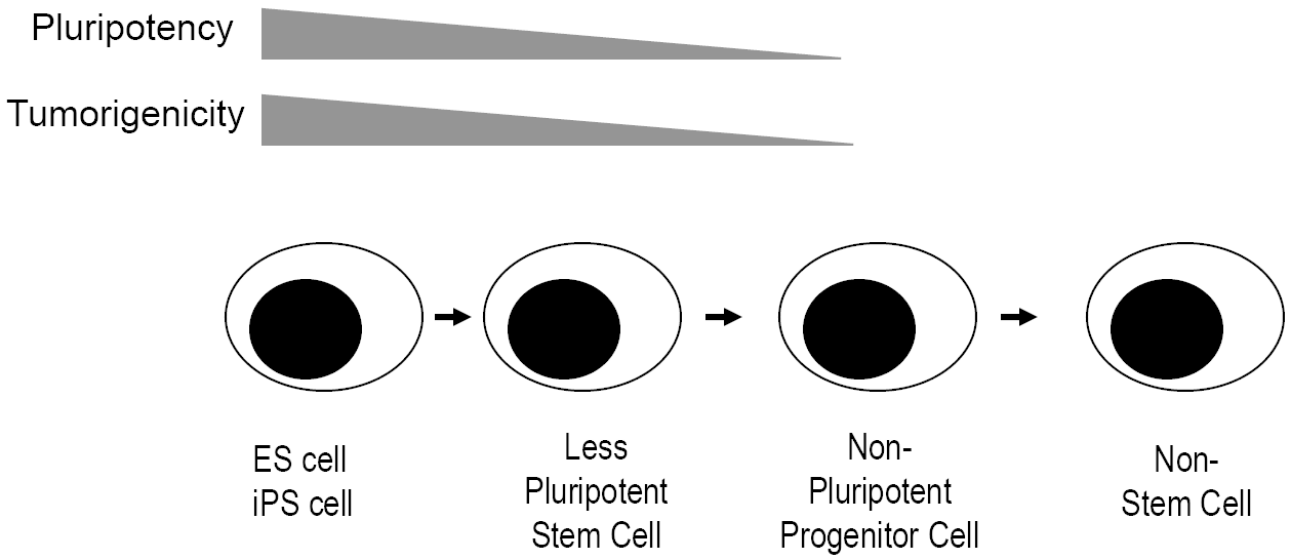

Figure 1.
Relationship between pluripotency and tumorigenicity in regenerative medicine. The capacity of stem cells to induce tumors in the host is directly proportional to their pluripotency.

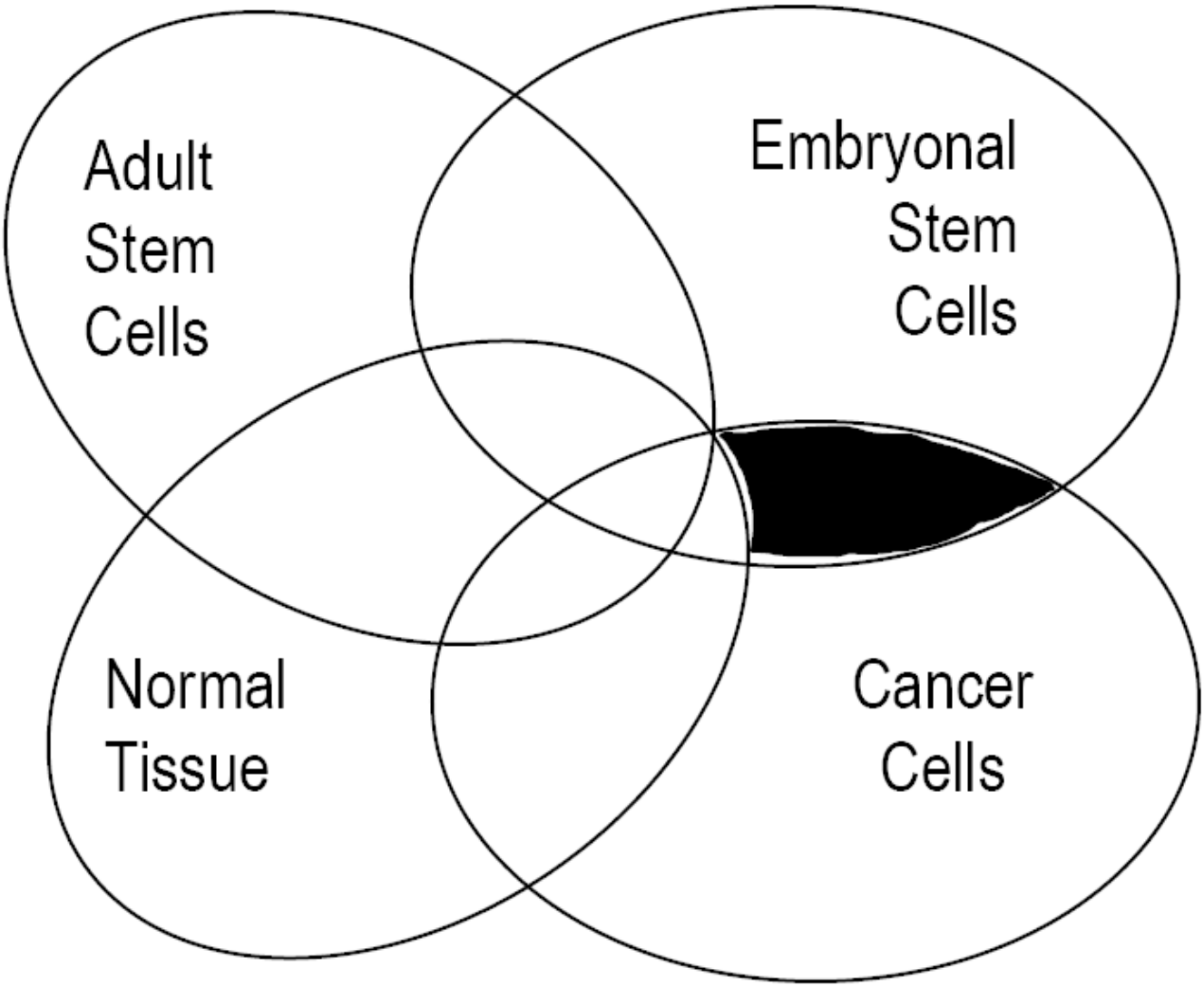

Figure 2.
Embryonal stem cell antigens as targets of cancer immunity. Genes restricted to ES cells and cancer, but not expressed by normal adult stem cells or their differentiated progeny (shaded area) may be potential targets for cancer vaccines. Some of these genes can regulate stemness in both cancer and ES cells, and are the most attractive targets.