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Stem Like Cells and Androgen Deprivation in Prostate Cancer

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1. Introduction

Cancer stem cells (CSC) have been hypothesized to contribute to tumor initiation and recurrence, but the very existence of CSC is currently under debate. Increased expression of stem cell markers in cancer tissues after various treatments has been observed in both experimental animal models and patients for a number of cancer types. Cancer cells that express stem cell markers are generally called stem-like cells (SLC) since the exact origin of these cells is often not clear.

Using human LNCaP prostate cancer cell-based mouse xenografts as well as a transgenic model of prostate cancer (TRAMP), we studied the possible origin of SLC and their potential role in cancer recurrence after androgen deprivation therapy (ADT). We found that the proportion of SLC within a tumor can change over time, particularly after anti-cancer therapy (Tang et al., 2010). A significant increase in the SLC population occurred in tumors soon after ADT (surgical castration), but then returned to basal levels when the tumors resumed growth after the initial response to ADT. Several stem cell markers were found to be elevated during this period. This phenomenon was observed in both LNCaP xenografts and in TRAMP mice. These observations suggest that ADT may induce a 'stemness' stage in tumors which, although transient, could allow tumor cells to adapt to the anti-tumor effects of ADT and enhance their survival. A similar phenomenon was observed in LNCaP xenografts after docetaxel treatment. We believe stemness may have a biological function in self protection; it may be one pathway by which tumor cells can survive and recur after anti-cancer treatment.

2. Cancer stem cell or cancer cell stemness

The concept of cancer stem cells (CSC) is built upon the hypothesis that tumor tissues harbor a very small population of cells that is responsible for tumor initiation and recurrence due to its capacity for self-renewal and multilineage differentiation, as well as relative drug resistance. However, the frequency of CSC can be highly variable among different tumor types, and even among tumors of the same type (Visvader & Lindeman, 2008). For instance, in clinical samples, the CSC population in melanomas (ABCB5^{+}) ranges between 1.6 - 20% (Schatton et al., 2008), and in colorectal carcinomas (CD133^{+}) between 1.8 - 24.5% (O'Brien et al., 2007). The factors governing the different frequencies of CSC within

tumors are not clearly delineated, although communication with surrounding cells and stroma, alterations in pH, chemokines/cytokines in the microenvironment, locoregional angiogenesis, and host response to local tissue damage could all potentially affect the CSC population to varying degrees.

A number of cell surface markers have been used to identify CSC in human cell cultures and *in vivo* experiments, including CD44, CD133, and c-Kit, among others. The relevance of some of the common stem cell markers such as CD44 with respect to stem-cell like properties and growth characteristics, however, is not altogether clear, particularly in established long term cell culture lines. For instance, in human prostate cancer cell lines, CD44 has been used to identify CSC; isolated CD44+ cells from prostate cancer cell lines and xenograft tumors show stem-like functions in terms of self-renewal, clonogenicity, tumorigenicity, as well as tumor metastasis (Patrawala et al., 2006; H. Li et al., 2008). However, significant differences in CD44 expression can exist between various prostate cancer cell lines in culture. For instance, by flowcytometry, CD44+ cells can represent 80-90% of the population in PC3 and DU145 cell lines (Patrawala et al., 2006; H. Li et al., 2008), but in LNCaP they are undetectable. The side population (SP) assay, which is based on exclusion of vital dyes, has also been used to identify a small subpopulation of cells enriched in self-renewal function particularly that derived from the bone marrow (Goodell et al., 1996). No difference in SP fractions is observed among PC3, DU145 and LNCaP cell lines, and their relevance to the overall biology of these cancer cells is not clear.

A recent comprehensive analysis of stem cell makers in the NCI60 Tumor Cell Line Panel demonstrates the presence of these various markers, but they are expressed in rather complex combinatorial patterns in cancer cell lines of different lineages (Stuelten et al., 2010). This and other studies suggest that established immortal cancer cell lines harbor SLC subpopulations, but also underscore the complexity of stem cell biology. Although mounting evidence supports the existence of CSC in various types of tumors (Baker, 2008; Dalerba et al., 2007; Lobo et al., 2007; C. Tang et al., 2007; Huntly & Gilliland, 2005), how cells with stem cell like-properties affect the growth characteristics and/or metastatic potential of tumors still remains an open question (Dalerba et al., 2007; Fabian et al., 2009; Jordan, 2009; Marotta & Polyak 2009; Clevers, 2011).

Another term, stemness, is frequently used in stem cell studies, but its exact definition has not been universally accepted (Leychkis et al., 2009; Hoffmann & Tsonis, 2011). Epithelial-mesenchymal and mesenchymal-epithelial transition states are also relevant not only to embryogenesis but to tumorigenesis; how these may relate to stemness is an area of active investigation ((Yang & Weinberg, 2008). In general, stemness represents a *state* in which cells are characterized by self-renewal and plasticity. In cancer tissue, the stemness state may be a transiently acquired property by a subpopulation of tumor cells that likely also involves input from surrounding cells. Biological or pharmacological stress, or changes in the tumor microenvironment, could serve as potential triggers for inducing this state, which may then allow for adaptation, survival and eventual disease progression.

3. Anti-tumor therapy and stem like cells in prostate cancer

Over the last several years we have utilized an LNCaP-based xenograft model and a genetically engineered transgenic mouse model, TRAMP, to study the effects of androgen

deprivation and chemotherapy on prostate cancer (Y. Tang et al., 2006, 2008, 2009, 2010). Tumor tissues were collected at different time points before and after various treatments, and the expression patterns of several stem cell markers were evaluated in an effort to better understand treatment response and potential mechanisms of tumor recurrence.

3.1 LNCaP xenograft based studies

LNCaP is a hormone-sensitive human prostate cancer cell line. Withdrawal of androgens *in vitro* interrupts its growth and induces apoptosis. *In vivo*, LNCaP tumors in male SCID mice cease growth for up to 2-3 weeks after surgical castration (bilateral orchiectomy), which is invariably followed by accelerated tumor growth (Figure 1A). Immunohistochemical (IHC) analysis of proliferation-related (Ki67) and angiogenesis-related (CD105) markers in castrated and non-castrated mice is shown in Figures 1B and 1C. It is apparent that a significant decrease in overall proliferation occurs only in the castrated mice between one and two weeks after castration, followed then by recovery of proliferative potential. This recovery of cell proliferation appears to parallel increased angiogenesis, which is observed at the IHC level between two and three weeks post castration. In non-castrated mice, on the other hand, tumors continue to grow unabated over time, with no observable changes in cell proliferation or overall angiogenesis noted over this period of continued growth (Figures 1A-C).

To determine whether SLC play any role in the above model, we also studied several stem cell markers. Recent studies suggest that SLC are a heterogeneous population with diverse biological properties, and that multiple subpopulations with stem cell-like characteristics can coexist in the same tumor (Hermann et al., 2007; Ma et al., 2008; Hope et al., 2004). Since there is no single specific 'standard' marker for identifying cancer stem cells, we selected several antigens that have been implicated in one way or the other in stem cell biology; specifically, CD44, CD133, and c-Kit (CD117) for IHC studies, and human ALDH (aldehyde dehydrogenase), Shh (sonic hedgehog), p63, BCRP (breast cancer resistant protein), Notch1 and bcl-2 for western blot analyses. Tumor samples were collected at days 5, 10, 15, 20, 25, and 30 post castration, and tumors from non-castrated mice collected at similar time points served as controls.

By IHC, expressions of c-Kit (Figure 1D) and CD44 (Figure 1E), but not CD133, were significantly increased in LNCaP xenograft tumors at the day 15 time point after castration but not at other time points in either castrated or control mice. Representative images of c-Kit and CD44 at day-15 (Cas-15) and day 30 (Cas-30) are shown in Figure 1E. Interestingly, we noted that the distribution of CD44+ and c-Kit+ cells in tumor tissues was different. Most of the CD44+ cells were found in the periphery of tumor islands, whereas c-Kit+ cells were present within the tumor mass (Figure 1E). This suggests that these two proteins can be expressed in different cells within the LNCaP tumors, and may potentially signify the presence of different subtypes of SLC in these tumors. In untreated control mice, on the other hand, SLC markers do not change significantly over time despite continued tumor growth, as shown in Figure 1D.

Data for several proteins evaluated by western blots are summarized in Table 1. It is apparent from these initial studies that there is a trend for Shh, Notch, ALDH, BCRP and p63 to be over expressed at least 2-fold at day 15 compared to the other time points post castration in most or all the tumor samples tested, while Bcl2 is over expressed in 2 of the 4 tumors evaluated at this time point.
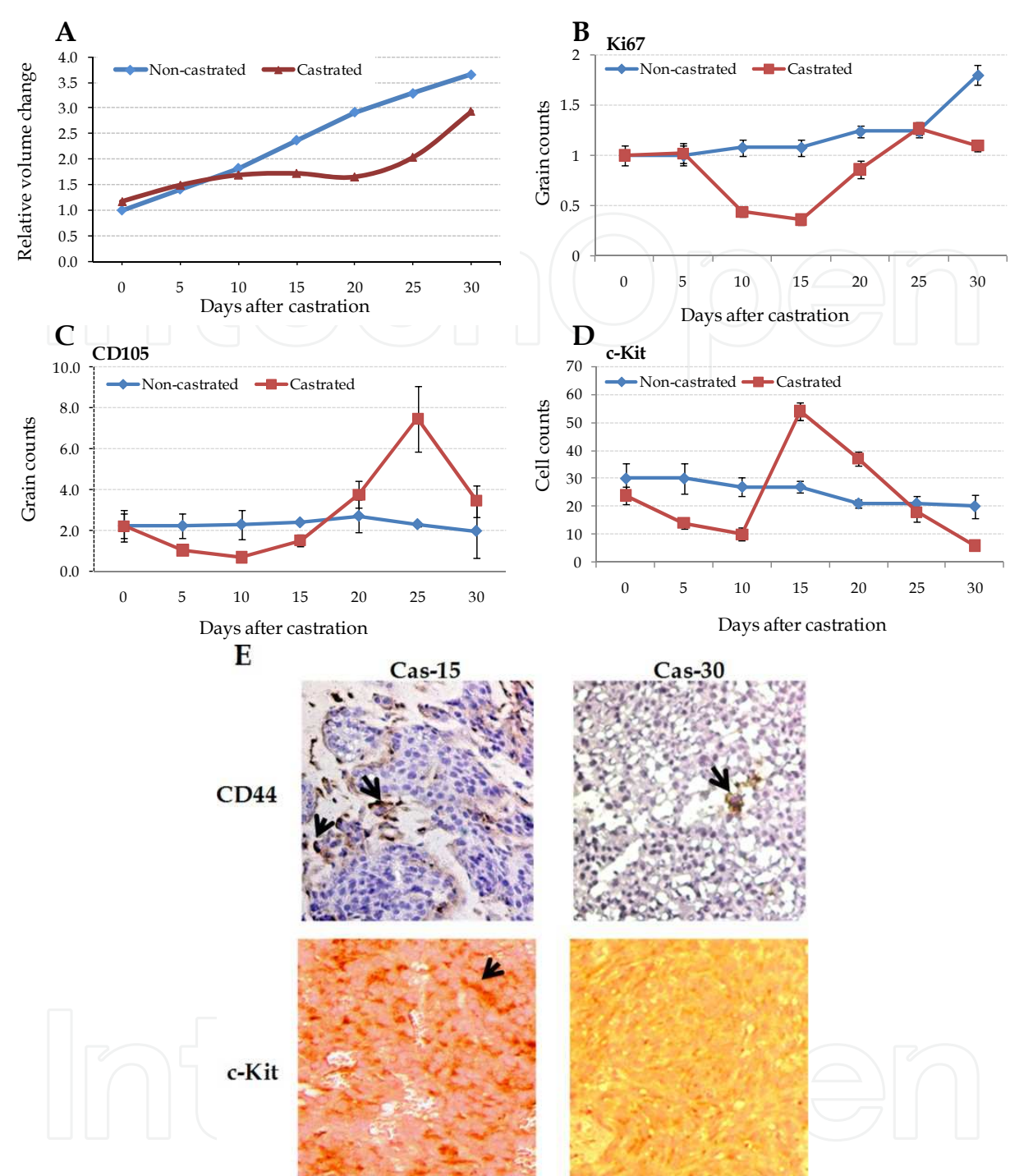
A. *Relative tumor volumes at different time points. Male SCID mice (6-8 wks of age), were inoculated sq with 5 x 10^6 LNCaP cells per flank. The tumor volumes are shown as the average tumor volume at each time point (5-10 mice) divided by the average tumor volume at day 0.* **B-D**. *Protein expression patterns are summarized as histographs based on IHC data. Cryosections or FFPE (formalin-fixed paraffin-embedded) tissue sections of tumors from each time point (n=4-5) were analyzed for the expression of Ki67 (**B**), CD105 (**C**), and c-Kit (**D**). Five to ten images per section were taken randomly and digitized using the autoscan function of MCID 7.0 software which was set with respect to grain counts (CD105, Ki67) or positively staining cells (c-Kit). Data were analyzed using SigmaPlot. E. Representative images demonstrating expressions of CD44 and c-Kit in tumors at days 15 (Cas-15) and 30 (Cas-30) post castration. (Amplification: 200x).*

Fig. 1. Evaluation of LNCaP tumors in castrated and non-castrated mice.

We also carried out pilot studies with docetaxel chemotherapy in the LNCaP xenografts (Figure 2). Specifically, LNCaP-bearing SCID mice were treated with docetaxel when tumour volumes reached approximately 300 cc (docetaxel was given IP at 8 mg/kg every 3 to 4 days X 4 doses over a two week period). Tumors were harvested from the mice at
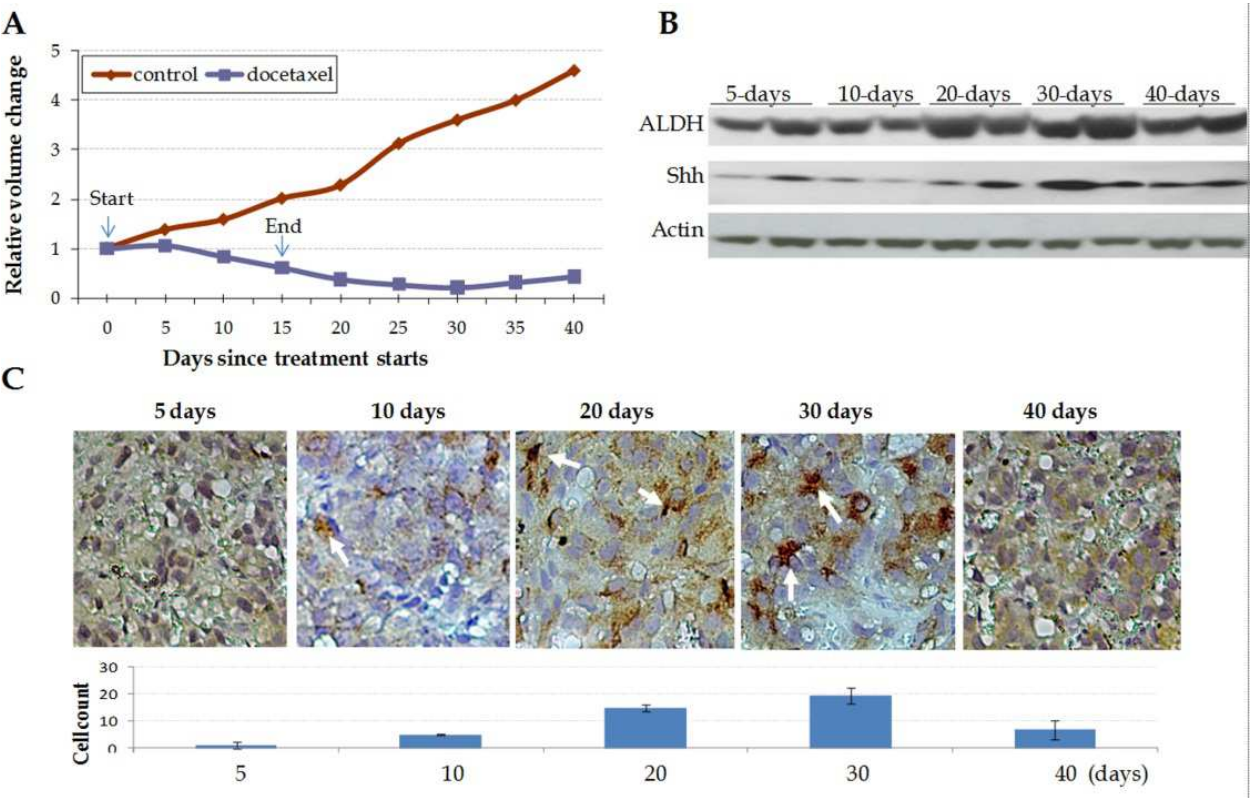
A. *Tumor volumes at different time points. Arrows indicate start and end of docetaxel treatments.* **B**. *Representative western blot. Expressions of ALDH and Shh at different time points from start of treatment were determined in tumor samples (n=5 per time point).* **C**. *IHC. c-Kit expression in various tumor tissues. The selected images are representative of 3-5 tumors per time point. Five to 10 images per slide were taken and digitized using MCID 7.0 software. Data were analyzed with SigmaPlot and plotted using Microsoft Excel.*

Fig. 2. Evaluation of LNCaP tumors in docetaxel-treated mice.

|	Day-5	Day-10	Day-15	Day-20	Day-25	Day 30
ALDH	0/6	0/6	6/6	3/6	0/6	0/6
Shh	0/6	0/6	6/6	0/6	0/6	0/6
Notch	0/6	0/6	4/6	0/6	0/6	0/6
p63	0/4	ND	4/4	ND	ND	0/4
BCRP	0/4	ND	4/4	ND	ND	0/4
bcl-2	0/4	ND	2/4	ND	ND	0/4

Equal amounts of protein from 3-5 tumors at each time point were analyzed with western blots. After normalization to β–actin, at least double the mean of the band intensities with respect to the non-castrated control samples in each reaction was considered to be overexpressed. ND: not done.

Table 1. The expression of stem cell markers in LNCaP xenografts post castration.

different time points post docetaxel treatment as shown in Figure 2A, and evaluated for ALDH and Shh expression by western blots and for c-Kit expression by IHC (Figures 2B and 2C). Although our analysis is limited, interestingly, as is the case with castrated mice, increased levels of ALDH, Shh and c-Kit were observed in the docetaxel treated mice at points of maximal anti-tumor response (Figures 2A-C). These initial studies suggest that docetaxel treatment can also induce enhanced expression of some of the proteins associated with SLC, although the kinetics of this response are somewhat different than observed in tumors from castrated mice. Thus, there is a trend towards enhanced expression of SLC-related proteins in both castrated mice and docetaxel treated mice at points of maximal anti-tumor response (i.e. when tumors are at their smallest sizes).

3.2 TRAMP based studies

A similar phenomena of enhanced SLC expression post castration was also observed in the TRAMP model in which probasin promoter-driven T antigen expression in mouse prostatic epithelia induces prostate cancers in male mice as they mature sexually (by 8 to 12 weeks of age)(Greenberg et al., 1995; Y. Tang et al. 2008).
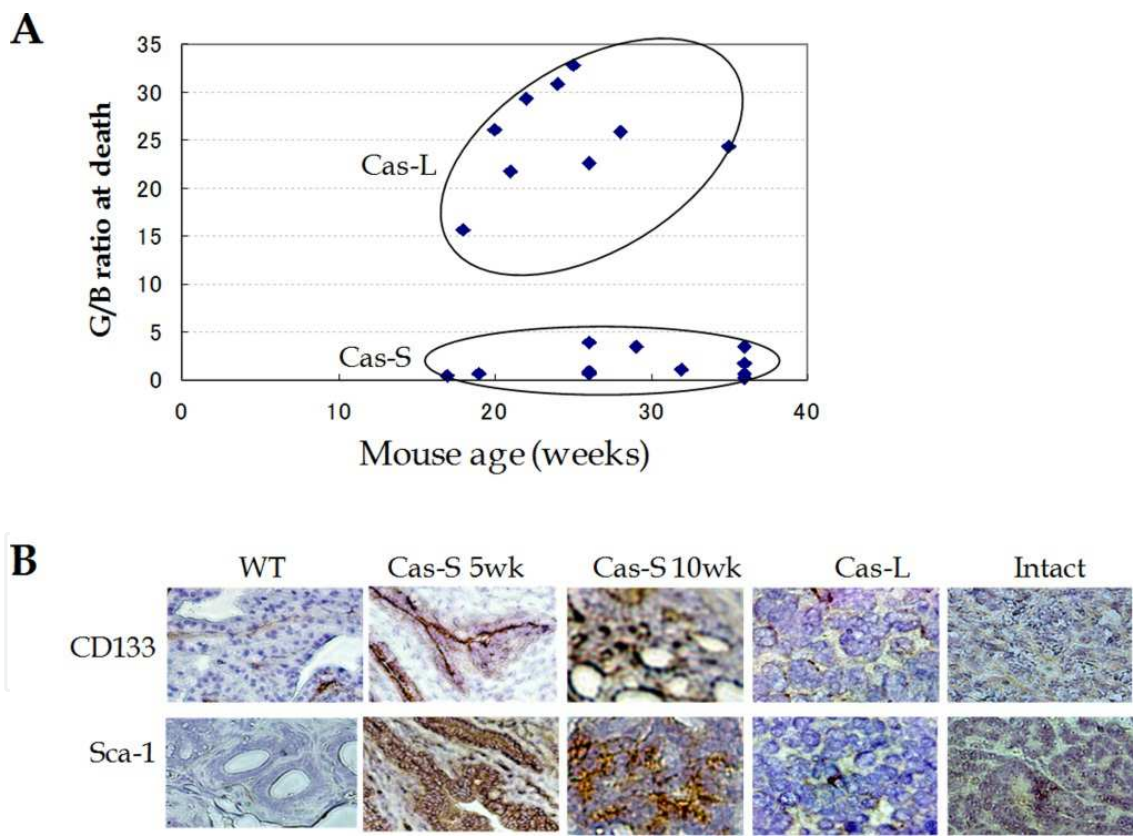
A. *Effects of castration on genitourinary (GU) organs. Based on G/B ratios (GU organs versus mouse body weight), TRAMP mice were divided into two groups after castration – those with G/B ratios ≤ 3.0 (Cas-S) and others with G/B ratios > 20 (Cas-L).* **B**. *IHC. Expressions of CD133 and Sca-1 in TRAMP mouse prostates. These proteins are highly expressed in Cas-S tumors around 5 (Cas-S 5wk; n=3) and 10 wks (Cas-S 10wk; n=3) post castration, but not in Cas-L tumors (n=3). Prostate tumors from non-castrated mice (intact; n=3) and normal prostate tissues from wild-type siblings (n=3) served as controls.*

Fig. 3. Evaluation of tumors in TRAMP mice.

We previously reported that castration of these mice at 12 weeks of age resulted in two different outcomes with respect to anti-tumor response (Y. Tang et al., 2008). In one group of mice, significant locoregional disease progression occurred subsequent to the castration without any evidence of tumor shrinkage such that the mice ended up with large prostatic tumors (designated Castration-Large or Cas-L); in these mice, the average genitourinary (GU) organ weight (which included prostate gland and seminal vesicles) to total body weight (G/B) ratios were 25.43 ± 5.25 (Figure 3A) (Y. Tang et al., 2008). Other mice (designated Castration-Small or Cas-S) had a positive response to castration in that prominent shrinkage of the prostate gland and other GU organs occurred so that the average G/B ratios were around 1.41 ± 1.31 (Figure 3A); despite a positive response to castration the prostate glands still harbored cancer cells. Analysis of two SLC markers, Sca1 (which is mouse-specific) and CD133, in mice responding positively to castration (i.e. small G/B ratios) revealed significant increase of both markers at weeks 5 (Cas-S 5wk) and 10 (Cas-S 10wk) (Figure 3B). By contrast, in Cas-L tumors and in tumors from non-castrated mice, Sca1 and CD133 levels remained low (Figure 3B).

4. Discussion

The above studies indicate that enhanced expression of SLC-related proteins can occur in prostate tumors in response to anti-proliferative/cytotoxic treatments such as androgen deprivation or chemotherapy. Further, this SLC response appears to be transient in nature in that it is generally limited to the time period of maximal anti-tumor response to treatment.

The increased expression of these SLC-related proteins observed in our tumor samples could be due to more proteins being expressed per cell but within a limited number of the cells, or alternatively more cells that express these proteins (but not necessarily at significantly higher levels than baseline) may be recruited, or it could be a combination of these two processes. Regardless of the specifics of the underlying processes associated with each individual protein in terms of patterns and mechanisms of expression, our results indicate that the *overall* expressions of several SLC markers in tumors change as a function of time post treatment. These transient elevations of a relatively broad range of stem cell markers indicate a complex tissue response in which not only tumor cells but other surrounding cells could be involved. We hypothesize that this transient period represents a stemness stage during which cancer cells and surrounding cells can adapt to a changed microenvironment.

Elevations of stem cell related proteins have also been observed by others. For instance, CD44 over expression in breast cancer patients after chemotherapy (X. Li et al., 2008), CD133 over expression in human glioblastoma after radiation (Bao et al., 2006), and ALDH1 over expression and increased enzyme activity in human colorectal xenograft tumors after chemotherapy (Dylla et al., 2008) have been reported. Other forms of stress such as hypoxia and products of metabolism, including lactate and ketones, have also recently been shown to induce stemness in tumor tissues (Kim et al., 2009; Martinez-Outschoorn et al., 2011). Thus, emerging data suggest a correlation between SLC and anti-cancer therapy or other forms of cellular stress, although the exact role of the SLC population in tumor recurrence remains unclear.

Xin et al have shown that prostate glands in C57BL6 wild type mice undergoing castration are enriched in Sca1+ cells, and which are found primarily in the relatively treatment-resistant G0 phase of the cell cycle (Xin et al., 2005). These cells are capable of regenerating tubular structures containing basal cells and luminal cells in a dissociated prostate

regeneration system, demonstrating their plasticity and role in prostate regeneration. Moreover, enriched SLC populations have been reported in several tumor-free tissues following local damage (Beltrami et al., 2003; Amcheslavsky et al., 2009). Thus, stemness may represent a protective response by tissue cells, including cancerous cells, to damage or environmental change. This stemness state may in turn allow cells to survive, adapt and grow. Stemness is not an unusual characteristic; many cells possess this ability. As indicated by Zipori et al, all cells possess the molecular machinery that enables them to return to a relatively undifferentiated stem cell-like state when appropriately challenged (Zipori, 2009). Several recent studies have also documented de-differentiation in mature cells (Brawley & Matunis, 2004; Monje et al., 2010; Red-Horse et al., 2010; Shoshani & Zipori, 2011) During tumor recurrence/progression, the de-differentiated SLC can re-differentiate back into the original tumor, or under other conditions, they could trans-differentiate to a different phenotype. Our TRAMP mice castrated at 12 weeks of age all eventually developed prostate cancer, including distant metastasis in over 70% of the animals (Y. Tang et al., 2008, 2009). In several of these mice, neuroendocrine carcinoma (NEC) partially or completely replaced the original adenocarcinomas in the prostate gland and/or distant metastatic sites (Y. Tang et al., 2009); this was rarely observed in the non-castrated mice. Thus, in TRAMP mice regrowth after castration can lead to 'differentiation' along the same original adenocarcinoma pathway or trans-differentiation along the NEC pathway.

A recent study showed that certain differentiated cells in breast tissue *spontaneously* converted to a stem cell-like state (Chaffer et al., 2011). This challenges the scientific dogma that differentiation is a one way path, i.e. once cells specialize they cannot return to a SLC state on their own. Thus, a considerable degree of plasticity exists among cells in their ability to reprogram themselves to a more permissive state not only when appropriately challenged, but under certain conditions this seems to occur spontaneously. The state of 'stemness' that occurs in response to androgen deprivation in our xenograft and transgenic prostate cancer models appears to be transient. Interestingly, recent work has shown that cancer cells in culture exposed to various drugs can undergo histone deacetylation mediated chromatin changes that result in transient reversible drug tolerant states (Sharma et al., 2010).

5. Conclusion

The transient nature of various adaptive responses noted above suggests that to maximize anti-cancer treatments, not only more effective agents need to be developed, but also the relative timing of these treatments with respect to the transient cellular states need to be taken into account. Thus, given that various adaptive cellular processes are dynamic, real time detection and targeting of cancer cells undergoing de-differentiation may improve the efficacy of anti-cancer therapies.

6. Acknowledgment

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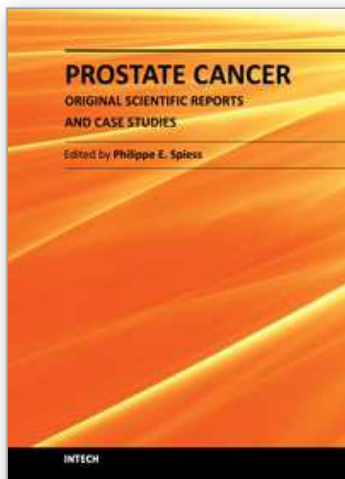
Prostate Cancer - Original Scientific Reports and Case Studies

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