Editorial
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Cancer Stem Cells "The Root of Radioresistance" in Prostate Cancer Radiotherapy

Prostate cancer (CaP) is a main health problem for older men in Western countries as well as in Australia. Radiotherapy (RT) continues to be an important treatment option for CaP patients detected at an early-stage or advanced-stage disease. Up to 20% of localized CaP are considered high-risk cases, as defined by clinical cT3–4 or Gleason score 8–10, or a baseline prostate specific antigen (PSA) >20 ng/mL. For high-risk cases, surgery or RT alone yields to higher rates of local relapse,[1] which may result in cancer progression to metastatic disease. One reason for these failures following RT is due to the radioresistance of a subpopulation of CaP clones within the tumor. RT dose escalation techniques have been used to counteract the radioresistance. Thus, radioresistance is a major challenge in current CaP radiation therapy.

Recently, the cancer stem cell (CSC) theory has offered a potential explanation for the relapse and resistance that occurs in many tumors after therapy. The theory states that tumors are heterogeneous and that the growth of tumor is driven by a discrete subpopulation of cells. CSCs (also called tumor-initiating cells) are defined as a tumorigenic cell that has the ability to recapitulate a heterogeneous tumor upon transplantation and may produce tumors through the stem cell processes of self-renewal and differentiation into multiple cell types. These CSCs could provide a reservoir of cells that cause tumor recurrence after therapy.[2]

CSCs are becoming recognised as being responsible for metastasis and radioresistance, and thought to be in a relatively quiescent state, therefore evading radiotherapeutic challenges and 'protecting' the continuity of the tumor. The CSC model has clinical implications, in that CSCs have been known to contribute to radioresistance predominantly through enhanced levels of DNA repair activity and slow cell cycle kinetics. However, what is still relatively unknown is how these cells develop and just exactly 'when' they originate. It still remains to be established whether the CSC is a function of a specific cell type, the micro-environment, epigenetic and genetic changes, or the stage of the tumor.[3] However, recent studies suggest that stimuli from tumor cells and immune cells cause cancer cells to dedifferentiate into cells with the ability to self-renew and to eventually migrate to distant sites. Progression of cancer cells to CSCs with a proportion of these cells will progress through the epithelial-mesenchymal transition (EMT) and metastasize. This complex process is slowly being fully elucidated and this knowledge will assist with the generation of more effective therapies which will control and may even eradicate cancer in the future.

CSCs embody the refractory nature observed among many cancers: very competent initial tumor establishment, extremely aggressive metastatic nature, resistance to chemo- and radiotherapy, correlation with advanced disease and resistance to current therapies. Therefore, if CSCs survive after anti-cancer treatment, recurrence and metastasis are expected due to the ability of these cells to give rise to new tumor colony growth. Thus, investigation of CSCs has been a hot spot of basic cancer research and is rapidly expanding into many related aspects of cancer research, including radiosensitization.

There is considerable evidence to suggest that, under certain experimental conditions, CSCs exhibit radioresistant features.[4] CSCs have been associated with a number of molecular markers. Phillips et al. demonstrated that $CD24^{-/low}/CD44^{+}$ cells from MCF-7 and MDA-MB-231 breast cancer cell lines are more resistant to RT.[5] Bao et al. reported that radioresistant glioblastomas exhibit a higher percentage of CD133 expressing CSCs.[6]

As far as we know, data related with the CSCs and CaP radioresistance are very limited until now. Both CD44 and CD133 are the most frequently observed putative CSC markers in CaP. Cho et al. showed an increase in CSC markers (CD44, CD133, Nanog and OCT3/4) with long-term recovery (after 33-35 days of RT treatment) of LNCaP and DU145 CaP cells *in vitro*.[7] We have recently demonstrated that the down-regulation of CD44 using a small interfering RNA (siRNA) enhances radiosensitivity in CaP cells.[8] These data suggest that the combination of RT with a CSC-targeted therapeutic strategy may prevent local and distant recurrence of CaP.

It is increasingly clear that a dynamic and multifactorial process is involved in the response of CaP cells to

radiation. However, the main hurdle for investigating CSCs in radioresistance is the limitation of appropriate models available as CSCs are a dynamic process and the expression of CSC markers can be affected by many factors including tumor microenvironment. We have recently developed CaP-radioresistant (RR) cell lines using the maximum dose of radiation treatment and found that these CaP-RR cells can induce EMT, enrich CSCs such as cell surface markers (CD44, CD44v6, CD326, ALDH) and transcription factor (Nanog and Snail), easily form more spheres and activate the PI3K/Akt/mTOR signaling pathways, indicating that this RT-treated cells are a good model to mimic clinical condition and study the roles of CSCs in CaP radioresistance. This model is not only suitable for CaP radioresistance research but also useful for other cancers.

Despite the ongoing debate on the abundance and origin of CSCs, it is generally accepted that they represent the root of cancer that must be eradicated in order to cure cancer. A better understanding of the CSCs and their associated signaling pathways that regulate radioresistance will hopefully open new treatment strategies for CaP. The recent identity of CSCs has unlocked a new potential avenue for radiosensitivity research. Elucidating the role of CSCs in the cancer cells' response to radiation will enhance our understanding of CaP recurrence after RT, and may direct research towards novel and specific radiosensitization agents that target CSCs. In theory, if tumour and normal tissue stem cell regulatory pathways can be separately selectively targeted, then not only could CSCs be radiosensitized, but normal tissue stem cells could also be radioprotected to improve the therapeutic ratio.

We expect that there will be increased understanding of the intrinsic and extrinsic factors that control the plasticity and maintenance of the CSC state (e.g., expression factors, miRNA expression, post-translational modifications of molecules that control stem cell fate and niche factors that control stem cell renewal). It needs to be recognized that the complex mixture of radiosensitivity determining factors is probably highly dynamic during fractionated RT. Thus, the development of future therapeutic strategies based on targeting potential CSC radioresistance mechanisms must take into account these complex and dynamic processes, whereby different radioresistant pathways may be better targeted at different stages of therapy to reduce the dependence of dose escalation. In addition, it may differ between tumor types, as well as between different individuals' tumors within a tumor type. Furthermore, any therapeutic strategy in the long term will need to take into account the biological features that control CSC behavior allowing the implementation of personalization of therapy.

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REFERENCES

1. Thoms, J., Goda, J. S., Zlotta, A. R., Fleshner, N. E., van der Kwast, T. H., Supiot, S., Warde, P., and Bristow, R. G. (2011). Neoadjuvant radiotherapy for locally advanced and high-risk prostate cancer. *Nat. Rev. Clin. Oncol.* 8, 107–113.
2. Kong, D., Li, Y., Wang, Z., and Sarkar, F. H. (2011). Cancer stem cells and epithelial-to-mesenchymal transition (emt)-phenotypic cells: Are they cousins or twins? *Cancers (Basel)* 3, 716–729.
3. Gupta, P. B., Chaffer, C. L., and Weinberg, R. A. (2009). Cancer stem cells: mirage or reality? *Nat. Med.* 15, 1010–1012.
4. Eyler, C. E. and Rich, J. N. (2008). Survival of the fittest: cancer stem cells in therapeutic resistance and angiogenesis. *J. Clin. Oncol.* 26, 2839–2845.
5. Phillips, T. M., McBride, W. H., and Pajonk, F. (2006). The response of CD24(−/low)/CD44+ breast cancer-initiating cells to radiation. *J. Natl. Cancer Inst.* 98, 1777–1785.
6. Bao, S., Wu, Q., McLendon, R. E., Hao, Y., Shi, Q., Hjelmeland, A. B., Dewhirst, M. W., Bigner, D. D., and Rich, J. N. (2006). Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. *Nature* 444, 756–760.
7. Cho, Y. M., Kim, Y. S., Kang, M. J., Farrar, W. L., and Hurt, E. M. (2012). Long-term recovery of irradiated prostate cancer increases cancer stem cells. *Prostate* 72, 1746–1756.
8. Xiao, W., Graham, P. H., Power, C. A., Hao, J., Kearsley, J. H., and Li, Y. (2012). CD44 is a biomarker associated with human prostate cancer radiation sensitivity. *Clin. Exp. Metastasis* 29, 1–9.

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Yong Li was awarded his Ph.D. in 2000 at University of New South Wales, Australia, is a NHMRC Career Development Fellow (Level 2), Principal Scientific Officer at SESLHD, Head of the Cancer Research Program at Cancer Care Centre/Prostate Cancer Institute at St. George Hospital. Associate Professor Li's research program is aimed at investigate the mechanisms of prostate cancer metastasis and drug-resistance/radioresistance associated with tumour microenvironment or cancer stem cell (CSC)/epithelial-mesenchymal transition (EMT); (b): To investigate novel biomarkers from human body fluids for cancer diagnosis and monitoring cancer progression; He has published 70 research papers in peer-reviewed journals.

Paul Cozzi graduated from UNSW in 1990. He completed Urology training and obtained the FRACS in 1999. He has a major interest in clinical and laboratory based research and completed a Masters in Surgery in 1998. Dr. Cozzi obtained fellowship training in Urologic Oncology at Memorial Sloan Kettering in New York between 1998–2000 returning to Australia to take up a Senior Lecturer post at UNSW and St. George Hospital. Associate Professor Cozzi has published and presented papers maintaining an active research program at St. George Hospital.

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