available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Letter to the Editor

Re: Johan Lindberg, Anna Kristiansen, Peter Wiklund, Henrik Grönberg, Lars Egevad. Tracking the Origin of Metastatic Prostate Cancer. Eur Urol 2015;67: 819–22

We read with great interest the article by Lindberg et al [1]. By searching for metastatic-specific DNA alterations in several regions of the prostate, the authors identified the components that gave rise to metastases, namely, a noninvasive component within prostatic ducts and an invasive component with Gleason score 4 + 4 = 8, highly related to the intraductal carcinoma, although located at some distance.

Evolutionary algorithms

These findings give rise to a series of questions. Is it possible, for example, to predict cancer behaviour and prognosis based on intratumoural heterogeneity? The use of evolutionary algorithms in which individual cells are allowed to grow and evolve according to selection criteria may be useful in this setting. From an evolutionary point of view, normal and tumour cells should be considered as individual members of a population evolving and competing for survival [2]. But how can tumour cells overgrow normal cells? And how can tumour cells with metastatic potential overcome less aggressive cancer cells?

Malignant transformation is linked to the stepwise acquisition of mutations to oncogenes and tumour suppressor genes, leading to selective advantage of cancer cells. Time is a key factor, allowing cancer cells to duplicate and accumulate mutations. Increasing clone heterogeneity is associated with a greater capacity to resist changes in the tumour environment, leading to selection of more aggressive clones.

Interestingly, this evolutionary process has been elucidated recently by Gundem et al in a study based on whole-genome sequencing [3]. They demonstrated that metastatic prostate cancer spread is based on two main mechanisms: (1) the transfer of multiple cancer clones among different metastatic sites (ie, cross-metastatic seeding) and (2) the de novo monoclonal seeding of daughter metastases. Cross-metastatic seeding in response to therapy has also been demonstrated by Hong et al in a patient with lethal prostate cancer [4]. After treatment, the metastasis contained two distinct populations: one derived from the original clone and a clone derived from a distant metastasis.

Adaptive therapy

Changing tumour environmental conditions can induce cells to compete for nutrients and stimulatory factors. Chemotherapy as well as immune cells exert continuous selective pressure on the dynamic tumour system. Tumour response is often transient, and chemotherapy may fail because of the evolutionary capacity of tumour phenotypes to adapt to therapy-induced perturbations. In this scenario, *adaptive therapy* has been proposed. This strategy consists of continuous treatment modulation to maintain a fixed population of chemosensitive cells that can suppress the growth of chemoresistant cells [5].

The evidence of spatially separated clones in the primary tumour raises a question about their common origin. This hypothesis could be partially sustained by the recent evidence that tumour cells can spread their own fragments of genetic information through exosomes [5]. Because cancer exosomes can be captured from body fluids by targeting tumour-specific antigens, it is possible to recover genetic material from these vesicles. This could be used to assess genomic tumour complexity without performing a biopsy and to assess the presence of chemoresistant cells harbouring specific genetic variations.

Single-cell analysis

The multiclonality also raises the necessity of reconsidering association studies performed on resected cancer tissues, which consist of a pool of clones [6]. Should we use only single-cell polymerase chain reaction to perform association studies? Recent advances have provided the opportunity to investigate the complexity of biological systems at the single-cell level. High-throughput analyses of the genomes, transcriptomes, and proteomes of single cells may help better characterize several processes, including gene expression dynamics, tissue heterogeneity, and prostate carcinogenesis.

DOI of original article: http://dx.doi.org/10.1016/j.eururo.2014.09.006.

http://dx.doi.org/10.1016/j.eururo.2015.07.011

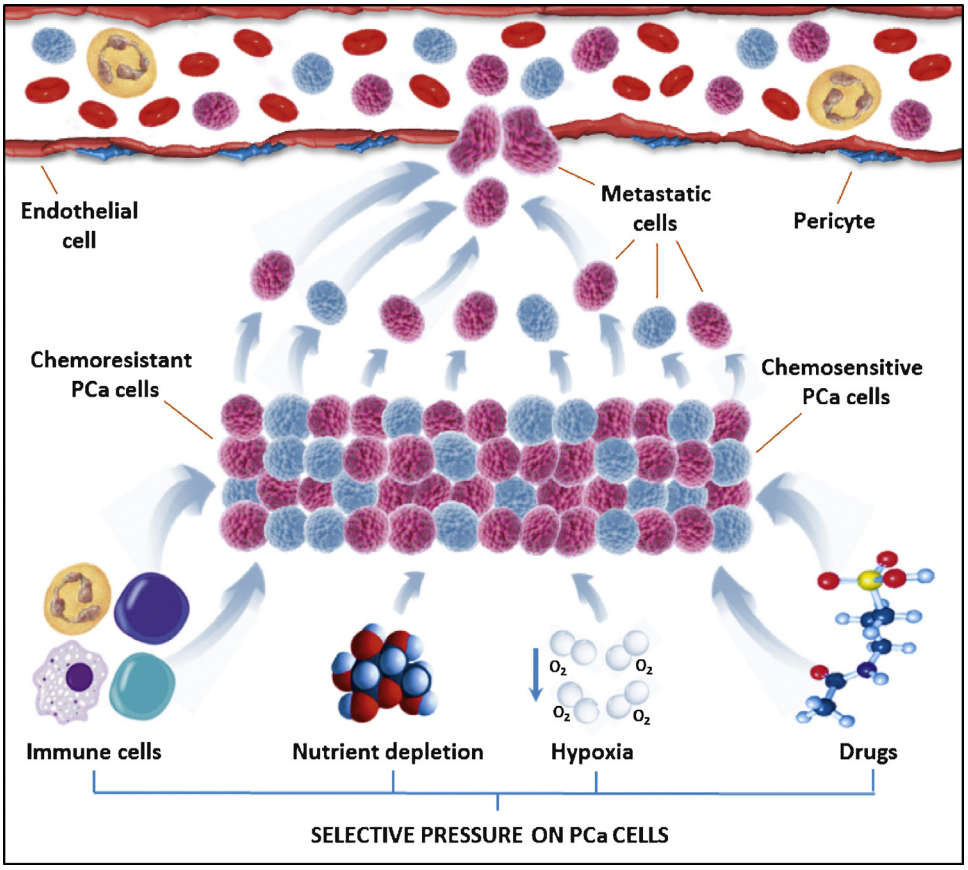

Fig. 1 – Selective pressure on prostate cancer cells. The sensitivity of prostate cancer cells to chemotherapy is the result of the selective pressure by several factors, including immune cells, nutrient deprivation, hypoxia, and cancer therapy.
PCa = prostate cancer.

In conclusion, advances in genomic testing [7] and modulating the equilibrium of the tumour environment in prostate cancer will be key issues in future years (Fig. 1). This research may lead to better integration of currently available interventions, including hormonal manipulation, chemotherapy, and emerging immunotherapy approaches.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Lindberg J, Kristiansen A, Wiklund P, Grönberg H, Egevad L. Tracking the origin of metastatic prostate cancer. Eur Urol 2015;67:819–22.
[2] Casás-Selves M, Degregori J. How cancer shapes evolution, and how evolution shapes cancer. Evolution (NY) 2011;4:624–34.
[3] Gundem G, Van Loo P, Kremeyer B, et al. The evolutionary history of lethal metastatic prostate cancer. Nature 2015;520:353–7.
[4] Hong MKH, Macintyre G, Wedge DC, et al. Tracking the origins and drivers of subclonal metastatic expansion in prostate cancer. Nat Commun 2015;6:6605.
[5] Gatenby RA, Silva AS, Gillies RJ, Frieden BR. Adaptive therapy. Cancer Res 2009;69:4894–903.
[6] Bryant RJ, Verrill C, Hamdy FC. The genomic diversity of prostate cancer: our Achilles heel explored. Eur Urol 2015;67:823–4.
[7] Boström PJ, Bjartell AS, Catto JW, et al. Genomic predictors of outcome in prostate cancer. Eur Urol 2015;68:1033–44.

Francesco Piva[a]
Matteo Santoni[b]
Marina Scarpelli[c]
Alberto Briganti[d]
Francesco Montorsi[d,e]
Rodolfo Montironi[c,*]

[a]*Department of Specialist Clinical and Odontostomatological Sciences, Polytechnic University of Marche, Ancona, Italy*
[b]*Medical Oncology, Università Politecnica delle Marche, Azienda Ospedaliero-Universitaria Ospedali Riuniti Umberto I, GM Lancisi, G Salesi, Ancona, Italy*
[c]*Section of Pathological Anatomy, Polytechnic University of the Marche Region, School of Medicine, United Hospitals, Ancona, Italy*
[d]*Department of Urology, IRCCS San Raffaele Hospital Milan, Milan, Italy*
[e]*Vita-Salute San Raffaele University, Milan, Italy*

*Corresponding author. Pathological Anatomy, Polytechnic University of the Marche Region, School of Medicine, United Hospitals, Via Conca 71, I–60126 Torrette, Ancona, Italy.
E-mail address: r.montironi@univpm.it (R. Montironi).

July 1, 2015