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DOI:
10.1016/j.eururo.2014.11.058

Document Version
Peer reviewed version

Citation for published version (Harvard):
Bryan, RT & Ward, DG 2015, 'Words of wisdom. Bladder cancers arise from distinct urothelial sub-populations', European urology, vol. 67, no. 3, pp. 590-1. https://doi.org/10.1016/j.eururo.2014.11.058

Bladder cancers arise from distinct urothelial sub-populations

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Nature Cell Biology 2014; **16**: 982–991.

Expert's Summary

Using lineage-tracing techniques to indelibly label urothelial sub-populations in BBN carcinogenesis mouse models, the authors found that papillary-like and CIS-like lesions developed from different urothelial cell populations: non-invasive papillary lesions from intermediate cells of the urothelium and CIS lesions from keratin-5 expressing basal cells. These findings support a model in which the heterogeneity observed in bladder cancers is determined both by genetic changes and the cell lineage from which the tumour originates. These findings also provide a plausible explanation for clinical observations in humans regarding differences in natural history and prognosis of patients with different types of non-muscle-invasive lesion, and suggest that the difference in clinical outcomes may stem, at least in part, from a fundamental difference in the cell of origin.

Experts' Commentary

"Bladder cancer or bladder cancers?" is a question that urological scientists have been asking for many years [1]: what are the molecular-genetic pathways that give rise to low-grade NMIBC, high-grade NMIBC, CIS and MIBC? Some genetic abnormalities are common to all urothelial bladder cancer (UBC) subgroups such as *TERT* promoter mutations, and others are associated with LG-NMIBC (*FGFR3* mutations) or HG-NMIBC/CIS/MIBC (*TP53* mutations). Previous studies have suggested that invasive or aggressive UBCs can develop from basal cells [2;3], and that some UBCs exhibit protein

and gene expression profiles indicative of an intermediate cell or luminal origin [4;5]. Van Batavia et al have now directly demonstrated that papillary and CIS/invasive lesions arise from distinct urothelial sub-populations, albeit in a model system which may not fully recapitulate tumourigenesis in the human bladder. It now seems increasingly likely that the context provided by the 'cell of origin' is key to both the oncogenic effects of the different genetic aberrations observed in LG-NMIBC and HG-NMIBC/CIS/MIBC and to the very different behaviours of these two types of UBC.

Many questions still remain. How do papillary tumours progress to MIBCs? Do papillary tumours always originate in the intermediate cell layer in humans? Why do patients seemingly successfully treated for organ-confined disease relapse and succumb? Where do G3T1 tumours with mixed mutation profiles originate? It is these fundamental questions that approaches based upon baseline tumour characteristics, rather than outcomes, are yet to answer. The authors do not discuss important processes such as epithelial-mesenchymal transition or the development of cancer stem cells, but their elegant utilisation of morphologic approaches is refreshing in the era of next generation sequencing and has contributed significantly to our understanding of this challenging disease.

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Acknowledgements

RT Bryan's research has been funded by the Medical Research Council (UK), Cancer Research UK, University Hospitals Birmingham Charities, and the University of Birmingham. DG Ward's research has been funded by Birmingham Science City, Cancer Research UK, University Hospitals Birmingham Charities, and the University of Birmingham.

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