



BLADDER CANCER

Root cause of bladder cancer revealed

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Researchers at Stanford School of Medicine have discovered the cellular origin of muscle-invasive bladder cancer. Kunyoo Shin, Phil Beachy and colleagues report their finding that invasive bladder cancer is derived from a single stem cell in *Nature Cell Biology*.

Previous studies have shown that a population of sonic hedgehog (Shh)-expressing basal urothelium cells can propagate and regenerate all types of urothelial cells, placing them as the likely candidates for bladder cancer stem cells. “This work paved the way for us to examine the general idea that stem cells might give rise to cancers in the specific context of the bladder, and that is the subject of our current study,” say Shin and Beachy in joint correspondence to *Nature Reviews Urology*.

Shin *et al.* used a mouse model of bladder cancer induced by the chemical carcinogen *N*-butyl-*N*-4-hydroxybutyl nitrosamine (BBN), which follows the same course as human disease. They performed two major experiments. First, they genetically marked the basal urothelial stem cells with GFP and found that all the resulting invasive tumours were also marked, implying that all muscle-invasive carcinomas are exclusively derived from these stem cells. Then, they ablated the stem cells and found that no tumours developed after BBN treatment, even when treatment was prolonged.

“In addition, we used a multi-colour fluorescent mouse—also known as the ‘Rainbow mouse’—to precisely determine the clonality and cellular origin of bladder cancer,” Shin and Beachy explain. “We found that the entire tumour, as well as surrounding

pre-malignant lesions, was labelled with one colour, indicating that a single stem cell takes over the lining of the entire urothelium during cancer progression, leading to the formation of a tumour originating from a single cell.”

Although Shh-expressing stem cells were responsible for the development of bladder carcinomas, Shh was not expressed in the advanced invasive tumours. The researchers highlight the importance of this observation, stressing that the properties of an advanced tumour might be considerably different from the cell of origin. “Even if you identify the tumour-propagating cells within a mature tumour, conclusions about the origins of a cancer based on properties of these cells may be inaccurate,” they warn.

The investigators also provide a potential explanation for the high recurrence rate of bladder cancer after surgery. They found that in the midst of cancer progression a single stem cell (and its progeny) can replace the entire bladder lining. This dysfunctional lining remains in place after the removal of invasive tumours and has a high probability of progression.

These findings set the scene for future studies; according to Shin and Beachy, they hope “to investigate the cellular and molecular basis for loss of Shh signalling and the functional role of that loss during progression of invasive urothelial carcinoma and metastasis.”

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Original article Shin, K. *et al.* Cellular origin of bladder neoplasia and tissue dynamics of its progression to invasive carcinoma. *Nat. Cell Biol.* doi:10.1038/ncb2956