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BLADDER CANCER

Genetic studies mark change in fortune for bladder cancer

It's been a long time coming, but the treatment of bladder cancer might be about to change for the better. Over the past few years it has become increasingly apparent that bladder cancer is lagging behind other urological malignancies in terms of awareness, funding, research, clinical trials and treatment options. Now, after 30 years without the approval of any new drugs, two genetic analyses provide a wealth of data on the molecular mechanisms of muscle-invasive bladder cancer, which are hoped to serve as the foundation for the development of new targeted treatments.

The first study, published in *Nature*, reports the findings of The Cancer Genome Atlas Research Network bladder cancer project, which was funded by the National Cancer Institute and the National Human Genome Research Institute, and performed by a large team of investigators at 40 institutions across the USA. "This project casts a spotlight on particular molecules and biological pathways that might serve as targets for a more individualized approach to therapy," says John Weinstein, co-leader of the project.

Tissue samples of 131 high-grade muscle-invasive bladder carcinomas, from patients who had not been treated with chemotherapy, were analysed for DNA alterations, RNA and protein expression changes, epigenetic variation and viral integration, to elucidate the genomic landscape of bladder cancer. Statistically significant recurrent mutations were found in 32 genes, many of which have not previously been detected in bladder cancer. Around half of the samples harboured mutations in *TP53*, and nine genes were identified that have not been reported to be significantly mutated in any other malignancy to date (*CDKN1A*, *ERCC2*, *RXRA*, *ELF3*, *KLF5*, *FOXQ1*, *RHOB*, *PAIP1* and *BTG2*). "These data provide a rich resource to the research community for interrogation and validation," Seth Lerner, project co-leader, told *Nature Reviews Urology*.

Integrated expression analysis identified four distinct subtypes of muscle-invasive bladder cancer, referred to as clusters I–IV. Cluster I tumours exhibit a papillary phenotype and *FGFR3* alterations. Along with cluster II tumours, they have features similar to luminal A breast cancer (expressing high levels of HER2 and luminal breast differentiation markers). Cluster III, on the other hand, has a gene signature similar to that of basal-like breast cancers and squamous cell cancers of the head and neck and lung. "These genomic similarities create a logical path to test targeted therapies from these other subtypes of cancer in blader cancer, rather than treating bladder cancers as one disease," explains Lerner.

In addition, alterations in chromatin-related genes were demonstrated in 89% of tumours, more than in any other cancer analysed to date, making bladder cancer a prime candidate for the new classes of chromatin-targeted drugs under development. Viral DNA was found in 6% of tumours, suggesting that viral infection might be involved in the development of a small percentage of bladder cancers.

According to Lerner, the investigators have at least 260 more tumours to analyse (bringing the total to over 400), which they hope will increase the power of the study to identify additional low-frequency significantly mutated genes. "We plan to validate the cluster analysis on external gene sets and the additional samples we have in the pipeline," explains Lerner. "The survival data is not mature enough for meaningful analysis, so we are working on updating the follow-up in order to determine if the subsets we identified are associated with outcome."

In a second, independent, study, published in *Proceedings of the National Academy of Sciences*, Carl Morrison and his team report a spectrum of genetic complexity, with two distinct classes of muscle-invasive bladder cancers at either end. They performed genomic analysis on five bladder tumours and matching germline blood samples, and validated their findings in >300 additional bladder cancer specimens.

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At the complicated end of the spectrum, they found that three of their original tumours harboured mutations in *TP53* and a large number of single-nucleotide variants (11.2 per megabase on average). These tumours were characterized by chromothripsis—thousands of simultaneous clustered chromosomal rearrangements. A second type of tumour with wild type *TP53*, no chromothripsis and a simple genotype was also elucidated.

Bladder cancer has been poorly served up until now, with the only available treatment options for muscle-invasive disease being surgery and chemoradiation, with no second-line therapies and no targeted treatments. Hopefully, these new findings signify a turning point in bladder cancer therapy.

Sarah Payton

Original articles The Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature* doi:10.1038/nature12965 | Morrison, C. D. *et al.* Whole-genome sequencing identifies genomic heterogeneity at a nucleotide and chromosomal level in bladder cancer. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1313580111