BLADDER CANCER

DNA changes can distinguish muscle-invasive from papillary tumors

Chromosome alterations that can differentiate invasive bladder tumors from their noninvasive counterparts early in disease development have been reported by a research group in Denmark, led by Karsten Zieger from Århus University Hospital.

Bladder cancer can be broadly divided into two basic forms: papillary, noninvasive lesions and solid, muscle-invasive tumors. A large proportion of cancers that present as noninvasive later develop invasive properties, though it is clinically difficult to predict which tumors these might be owing to a lack of early symptoms. Zieger and colleagues have identified a number of chromosome variations associated with carcinoma *in situ* (CIS)—the presumed precursor lesion of invasive bladder cancer—and demonstrated their mutual exclusivity with DNA changes observed in papillary tumors, suggesting the existence of two distinct molecular pathways of pathogenesis.

Initially, Zieger and his team used CIS cells isolated from patients with invasive bladder cancer to identify differences in chromosome copy number and loss of heterozygosity associated with CIS. Changes, found in 8 of the 12 samples, included copy number gains on chromosomes 5p, 6p22 and 10p15.1, and loss of heterozygosity on 5q12–q14. 5p gains were by far the most common variant detected.

Correlation of these variations with the CIS phenotype was confirmed in 48 high-risk (stage T1 and grade 3) non-muscle-invasive tumors, using single nucleotide polymorphism microarray technology; all 13 tumors with 5p gains also had CIS. Furthermore, CIS-associated chromosome changes and *FGFR3* mutations (a known marker of papillary cancers) were found to be mutually exclusive. "Based on this, we were able to classify high-risk non-muscle-invasive bladder tumors according to *FGFR3* mutations and chromosomal changes into papillary and CIS-type tumors" explains Zieger.

Zieger and colleagues are currently performing fluorescent *in situ* hybridization experiments to further validate their results, and suggest these findings might aid the development of molecular predictors of prognosis for patients with non-muscle-invasive bladder cancer.

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Original article Zieger, K. *et al.* Consistent genomic alterations in carcinoma *in situ* of the urinary bladder confirm the presence of two major pathways in bladder cancer development. *Int. J. Cancer* **125**, 2095–2103 (2009).