COMMENTARY

Centrosomal Proteins in Urothelial Tumors

New Pathways in Disease Pathogenesis

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Centrosomes are important cellular centers for regulation of transport to and from microtubules. One of the proteins that are implicated in regulation of organelles during the cell cycle is centrosomal protein (CEP) 72. CEP72 was found to be associated with the centrosome from dinoflagellates to human cells. More important, CEP72 shows a close homology with the heat shock protein 70, which is a part of the machinery responsible for protein folding and protection of stress. Another member of a centrosomal component is heat shock protein 90, which is localized at different stages of development of Drosophila and vertebrates. Thus, this chaperone participates in the process of centrosome assembly. Three-dimensional models of centrosomal proteins have been studied by Dos Santos and colleagues and are publicly available.

There is a need to investigate the role of centrosomal proteins in benign and malignant tumors. As Li and colleagues report in this issue of The American Journal of Pathology, CEP72 overexpression is associated with poor prognosis in patients with urothelial cancer. Patients’ tissues have been obtained at radical cystectomy. Because of the fact that efficient therapies for urothelium cancer are needed, functional studies have been conducted in the present article with the aim to understand the role of CEP in bladder malignancy. One of the previous reports led to the identification of CEP72 as a negative regulator of the tumor suppressor BRCA1 in colon cancer. BRCA1 mutations and other alterations have been studied in oncology to determine cancer risk and individualize therapy approaches. One of the important findings by Li and colleagues is the fact that CEP72 is expressed in a group of cell lines, thus pointing to different mechanisms related to bladder carcinogenesis. Clearly, other CEPs may have a role in the disease pathogenesis in cases in which CEP72 is not highly expressed. Correlation of its expression with tumor stage suggests that in a subgroup of patients, CEP72 may be a valid therapy target. Modulation of CEP72 by shRNA or overexpression demonstrated its involvement in regulation of migration and invasion. Consistent with in vitro results, overexpression of CEP72 yielded a higher metastatic potential in a mouse model. An effect on epithelial-to-mesenchymal transition, as observed by CEP72 knockdown and induced increase of E-cadherin and decrease in vimentin, was evident. The authors’ findings open new possibilities to examine effects of potential drugs that regulate epithelial-to-mesenchymal transition and cellular stemness in urothelium cancer.

An important aspect of the present study is the identification of serpin family E member 1 (SERPINE1), the main regulator of the plasminogen system, in CEP72 modulation. Patients with higher expression of SERPINE1 demonstrated a lower survival. Its promoter was enriched by the transcription factor cAMP response element-binding protein (CREB), along with the p300 transcriptional coactivator. The results presented by Li and colleagues, therefore, have some implications on future studies on these two proteins. In prostate cancer, the role of p300 and the related CREB-binding protein (CBP) has been analyzed in the context of androgen receptor signaling. They are increasingly expressed during androgen ablation therapy in prostate cancer. In turn, these two proteins enhance androgen receptor activity in the presence of androgens and antiandrogens. Interestingly, it was demonstrated that they induce migration and invasion not only in the presence of androgen receptor. Taken together, the results suggest...
possible interactions between centrosomal proteins and p300/CBP. The lack of mechanistic insights into p300 action in bladder cancer makes it an interesting area for investigations in the future.

One could consider future studies to include centrosomal proteins in molecular classification of bladder cancer. Classification is largely based on differences in gene expression, mutations, and histology.

It became clear that analysis of genomic and transcriptomic data could improve subclassification of these tumors. On the basis of recent findings, it has been suggested that combination of molecular pathology and global mRNA profiling is required for adequate subclassification of urothelial cancer. One could expect that analysis of data related to CEP expression will further improve molecular classification of urothelial tumors. For translational purposes, it is important to mention that Seiler et al postulated that molecular subtypes in muscle-invasive bladder cancer are a predictive factor after chemotherapy.

Signaling pathways of CEP72 involved in regulation of proliferation, migration, and invasion in urothelium cancer will likely be investigated in the future. In particular, identification of regulators of the cell cycle, such as specific kinases, may represent a research area of high interest.

References
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