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Commentary

Significance of Chromatin Alteration Complex in Bladder Cancer and their Beneficial Prospects

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DESCRIPTION

In normal and malignant cells, chromatin modifying enzymes regulate chromatin architecture and, by extension, the underlying transcriptional kinetics, primarily through post translational alterations. Changes in chromatin modifiers are common in Muscle Invasive Bladder Cancer (MIBC), with 76 percent of tumors showing a mutation in at least one chromatin modifying enzyme. Furthermore, in the normal urothelial, clonal proliferation of cells with inactivating mutations in chromatin modifiers has been seen, suggesting that these proteins play a role in bladder homeostasis that is currently unknown. Bladder cancer is the fourth most frequent cancer in men and the sixth most prevalent cancer in general, with an average diagnosis age of 73 years. The majority of Bladder Cancer (90 percent) results from unabated cell growth in the stratified urothelial, a specialized epithelial layer that borders the urinary system [1,2].

The nucleosome's basic structure is made up of 146 bp of DNA wrapped around a histone octamer with two molecules of H2A, H2B, H3, and H4. Post-Translational Modifications (PTMs) that affect chromatin structure are seen in tail-like structures projecting from core histones. All cellular activities, from cell division throughout organism development to uncontrolled cell division during neoplastic transformation, are influenced by chromatin packing and accessibility. Chromatin remodeling complexes, as well as DNA and histone modifying proteins, are examples of chromatin modifying proteins. Histone modifying proteins alter Post-Translational Modifications (PTMs) on histone tails, whereas chromatin remodeling complexes use the energy from ATP hydrolysis to reposition nucleosomes to increase accessibility of DNA binding proteins to DNA [3,4].

Methylation is a type of DNA modification that is dynamic, reversible, and non-sequence altering. It impacts the accessibility and transcription of DNA. DNA methylation, which is common at gene promoters, is linked to transcriptional silence. DNA methylation prefers cytosine's contained in palindromic CpG dinucleotide repeats. Unmethylated promoters containing CpG islands can be targeted by aberrant DNA methylation during cellular transformation, which is linked to tumor suppressor gene transcriptional suppression. DNA methylation patterns generated during tissue patterning and differentiation are carried on as epigenetic features across cell generations in a metastable process. DNA methylation-mediated gene silence has been found to be as common as, if not more common than, loss-of-function mutations as a mechanism of transcriptional repression in cancer. There is a link between smoking and the likelihood of acquiring Bladder Cancer, according to epidemiological studies. Studies of DNA methylation patterns in urothelial carcinomas have discovered a CpG island hyper methylator phenotype that is linked to cigarette smoking intensity [5].

Histone methylation occurs mostly at lysine and arginine residues on the positively charged tails of histones H3 and H4. The effect of the alteration on chromatin conformation and thus transcriptional status of the locus is determined by the placement of the methylation residue in the side chain and the number of methyl-groups present on the amino-acid residue. H3K4, H3K36, and H3K79 methylation is related with transcriptional activation, whereas H3K9 and H3K27 methylation is associated with transcriptional repression. H3K4me1 is abundant at enhancers, whereas H3K4me3 is found mostly at active promoters. Within normal urothelial, recent research studying early processes in bladder cancer discovered the clonal proliferation of cells with extensive somatic mutations in chromatin regulatory genes. The discovery of a high incidence of chromatin modifying enzyme mutations in multiple cohorts has heightened the need to better understand how these gene changes influence disease aggressiveness and predict treatment results in Bladder Cancer patients [6].

CONCLUSION

Chromatin modifying enzyme mutations are common in bladder Cancer, and numerous intriguing therapeutic strategies for altering these genes' activity are now being tested in clinical trials. More research into how the epigenetic landscape changes as the disease advances could aid in identifying people who would benefit the most from these tailored treatments.

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