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MOLECULAR PATHWAYS OF CARCINOGENESIS IN PROSTATE CANCER

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Prostate cancer is a highly prevalent malignancy in men, characterized by a wide spectrum of biological behavior ranging from indolent tumors to highly aggressive, metastatic disease. The molecular pathways underlying prostate carcinogenesis are complex and involve an interplay of genetic predisposition, somatic mutations, epigenetic alterations, and hormonal regulation. This complexity reflects the heterogeneity and multifocal nature of the tumor, making it challenging to identify a single unifying mechanism responsible for its development and progression.

The molecular basis of prostate cancer can be broadly understood through hereditary and sporadic mechanisms. Hereditary prostate cancer represents a smaller proportion of cases and is associated with familial clustering and earlier onset. Rather than being caused by a single gene mutation, it is typically the result of multiple low to moderate penetrance susceptibility genes, such as RNASEL, HPCX, ELAC2, and CHEK2. These genes are involved in critical cellular processes including DNA repair, apoptosis, and immune regulation. However, their individual contributions are modest, and environmental and lifestyle factors further influence disease risk.

In contrast, sporadic prostate cancer the majority of cases results from acquired somatic genetic and epigenetic alterations. Key tumor suppressor genes, including p53, PTEN, and RB, are frequently inactivated, especially in advanced disease. Loss of PTEN activates the PI3K/AKT pathway, enhancing cell survival and proliferation, while p53 mutations impair DNA damage induced apoptosis. Epigenetic silencing via promoter hypermethylation, particularly of GSTP1, represents an early and common event in prostate carcinogenesis.

Oncogenes further contribute to tumor progression by enhancing proliferative and survival signals. Overexpression of c-MYC is associated with aggressive disease and poor prognosis, while Bcl-2 promotes resistance to apoptosis, particularly in advanced and hormone refractory cancer. Growth factor signaling pathways, including those mediated by epidermal growth factor, insulin like growth factors, and interleukin-6, play significant roles in tumor growth, angiogenesis, and metastasis. Additionally, gene fusions involving ETS transcription factors, such as ERG, represent important molecular alterations that drive oncogenic transcriptional activity.

A defining feature of prostate cancer is its dependence on androgen signaling. The androgen receptor regulates the expression of genes essential for prostate cell growth and survival. Although androgen deprivation therapy is initially effective in controlling tumor growth, many cancers eventually progress to an androgen independent state. This transition is mediated by mechanisms such as androgen receptor mutations, amplification, and activation through alternative pathways, allowing tumor cells to continue proliferating despite low androgen levels.

In conclusion, prostate cancer carcinogenesis is a multistep and multifactorial process involving a network of molecular alterations that disrupt normal cellular homeostasis. Both genetic and epigenetic changes contribute to tumor initiation and progression, while hormonal influences play a central role in disease behavior. Understanding these molecular pathways is crucial for improving early detection, identifying aggressive forms of the disease, and developing targeted therapies. Continued research in this field holds promise for more effective and personalized approaches to the management of prostate cancer.