CHAPTER 7

CAVEOLIN-1 AND PROSTATE CANCER PROGRESSION

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Abstract: Caveolin-1 was identified in the 1990s as a marker of aggressive prostate cancer. The caveolin-1 protein localizes to vesicular structures called caveolae and has been shown to bind and regulate many signaling proteins involved in oncogenesis. Caveolin-1 also has lipid binding properties and mediates aspects of cholesterol and fatty acid metabolism and can elicit biological responses in a paracrine manner when secreted. Caveolin-1 is also present in the serum of prostate cancer patients and circulating levels correlate with extent of disease. Current evidence indicates that increased expression of caveolin-1 in prostate adenocarcinoma cells and commensurate downregulation of the protein in prostate stroma, mediate progression to the castration-resistant phase of prostate cancer through diverse pathways. This chapter summarizes the current state of our understanding of the cellular and physiologic mechanisms in which caveolin-1 participates in the evolution of prostate cancer cell phenotypes.

INTRODUCTION

Prostate cancer (PCa) is an androgen-sensitive malignancy that affects middle-aged or older men. PCa is the most common noncutaneous male cancer and a leading cause of cancer death in Western countries. At this writing, PCa claims about 28,000 lives per year in the US. Organ-confined prostate adenocarcinoma is essentially curable in the majority of cases by surgery or radiotherapy. However, there is no effective treatment for nonlocalized disease, which in the developed world generally emerges unpredictably.

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after a course of androgen suppression within several years after primary therapy begins. Once primary treatment has failed, there is no effective therapeutic strategy. Because hormone ablation is standard-of-care for nonlocalized disease, recurrence following therapy is characterized as the hormone-insensitive or “castrate-resistant” phase. Clinical progression leads to death within 5 years in most cases, even with aggressive therapeutic intervention. Limited advances in alternative chemotherapeutic modalities have been made in the past decade, however prolongation of survival in the context of the few reported successes against castration resistance has been extremely modest.

In the developed world, PCa is also greatly over-treated. About 70% of patients who receive therapy harbor cancer that would not be clinically threatening during their lifetimes. However, with current technology it is not possible to distinguish indolent cancers from those likely to progress. Many advances in this field are needed to identify new therapeutic strategies and targets that will improve overall survival, as well as quality of life for patients diagnosed with PCa. New biomarkers are also necessary to inform treatment decisions, especially as they relate to novel therapeutic approaches.

Caveolin-1 (Cav-1) is a 21-24 kDa multi-functional signaling protein and lipid transporter that has the distinction of being both a circulating PCa biomarker and a mediator of PCa progression. Cav-1 is the major structural protein within caveolae, small membranous organelles that reside in the cytoplasm or appear as invaginations of the plasma membrane. Cav-1 acts as a scaffold within these structures to organize numerous molecular complexes, thereby regulating a variety of cellular events. Alterations in expression of Cav-1 have been described in a number of malignancies. Increasing evidence points to a dichotomous role played by Cav-1 in cancer, with two prominent cases represented by breast and prostate cancer, in which Cav-1 seems to reduce and promote tumor growth, respectively. Therefore, the Cav-1 protein can be thought of as both a tumor suppressor and a tumor promoter, albeit in different contexts. In PCa, Cav-1 expression correlates positively with aggressive and metastatic potential and serum Cav-1 levels are elevated in patients with PCa but not those with benign prostatic hyperplasia. Several studies have also shown that Cav-1 is capable of actively promoting the metastatic and castrate-resistant phenotypes, suggesting it is not an innocent bystander during disease progression. Because of the diverse mechanistic roles played by Cav-1, its localization within plasma membrane microdomains where many oncogenic proteins also reside and because it circulates in the bloodstream at increased levels in advanced disease, the protein is an attractive focus for therapeutic intervention and biomarker development. The goal of this chapter will be to provide an overview of the current state of knowledge of cell signaling and metabolism in PCa as these processes relate to our understanding of the diverse functional roles of Cav-1.

THE ROLE OF ANDROGEN IN PROSTATE CANCER

Huggins and Hodges reported in 1941 that PCa is dependent on testicular androgens. Androgens are sterolic hormones that work by binding with high affinity to the androgen receptor (AR), a member of the class I subgroup of the nuclear receptor superfamily of transcription factors. The primary androgenic ligands for the AR are testosterone and its metabolite, 5α-dihydrotestosterone (DHT). DHT is the principal...