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Signaling Mechanisms of Vav3, a Guanine Nucleotide Exchange Factor and Androgen Receptor Coactivator, in Physiology and Prostate Cancer Progression

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Chapter 6
Signaling Mechanisms of Vav3, a Guanine Nucleotide Exchange Factor and Androgen Receptor Coactivator, in Physiology and Prostate Cancer Progression

Leah S. Lyons and Kerry L. Burnstein

Abstract The Rho GTPase guanine nucleotide exchange factor (GEF) Vav3 is the third member of the Vav family of GEFS and is activated by tyrosine phosphorylation. Through stimulation of Rho GTPase activity, Vav3 promotes cell migration, invasion, and other cellular processes. Work from our laboratory first established that Vav3 is upregulated in models of castration-resistant prostate cancer progression and enhances androgen receptor as well as androgen receptor splice variant activity. Recent analysis of clinical specimens supports Vav3 as a potential biomarker of aggressive prostate cancer. Consistent with a role in promoting castration-resistant disease, Vav3 is a versatile enhancer of androgen receptor by both ligand-dependent and ligand-independent mechanisms and as such impacts established pathways of androgen receptor reactivation in advanced prostate cancer. Distinct Vav3 domains and mechanisms participate in ligand-dependent and -independent androgen receptor coactivation. To provide a physiologic context, we review Vav3 actions elucidated by gene knockout studies. This chapter describes the pervasive role of Vav3 in progression of prostate cancer to castration resistance. We discuss the mechanisms by which prostate cancer cells exploit Vav3 signaling to promote androgen receptor activity under different hormonal milieus, which are relevant to clinical prostate cancer. Lastly, we review the data on the emerging role for Vav3 in other cancers ranging from leukemias to gliomas.

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Introduction

While major strides have been made toward understanding the molecular changes that accompany the development of castration-resistant prostate cancer, the critical factors and pathways that drive this process are still being defined. Early microarray analyses were conducted to compare differences between androgen-dependent LNCaP cells and their castration-resistant derivative, LNCaP R1 cell line (developed by Drs. Kokontis and Liao from the University of Chicago) by long-term culture of LNCaP cells in androgen-depleted media [1]. These experiments revealed that the expression of the *VAV3* gene is robustly upregulated in the castration-resistant LNCaP R1 line as compared to LNCaP cells [2]. Indeed, Vav3 exhibited the highest degree of upregulation in LNCaP R1 cells compared to all other genes in this screen. Vav3 gene expression is now known to be elevated in several models of castration-resistant disease progression [3–8]. As the third and newest member of the Vav family of proteins, Vav3, like the other Vav family members, serves as a guanine nucleotide exchange factor (GEF), for small Rho GTPases [9]. While the closely related founding member of the Vav subfamily of diffuse B cell lymphoma (DBL) GEFs is considered a proto-oncogene because a truncated version of Vav1 (originating from a cloning artifact) is transforming [10], Vav3 was recognized originally only as a Rho GTPase GEF. Much work has revealed a broad spectrum of physiologic actions of Vav3 and unexpectedly that Vav3 plays a key role in prostate cancer progression by serving as a versatile coactivator of the androgen receptor (AR).

Vav Domain Composition and Regulation of GEF Activity

Vav3 belongs to a small subfamily of DBL GEF proteins that includes the closely related founding member, Vav1 and the Vav2 proteins [9]. Tissue distribution of Vav proteins varies among the family members. Vav1 is expressed primarily in hematopoietic tissues, whereas Vav2 is expressed ubiquitously and Vav3 has a broad expression profile, which includes prostate, heart, brain, bone, kidney, pancreas, placenta, and breast [11, 12] and data deposited in public databases (http://genecards.weizmann.ac.il/genenote/; http://www.ncbi.nlm.nih.gov/unigene/; http://biogps.org/). The Vav family of proteins is structurally complex, consisting of multiple functional domains. These domains include (sequentially from the amino terminus): a calponin homology (CH) domain, an acidic domain (AD), a catalytic DBL homology domain (DH), which confers GEF function, followed by a pleckstrin homology (PH) domain, a cysteine-rich domain (also termed a zinc finger domain), and two src homology 3 (SH3) domains flanking a single SH2 domain (Fig. 6.1). As is true for all DBL family GEFs, the DH domain interacts directly with Rho GTPases and the DH and PH domains are arranged in tandem [9, 13]. For most DBL family GEFS, the PH domain modulates GEF activity through