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Vav1: Friend and Foe of Cancer

Fukun Guo and Yi Zheng*

Division of Experimental Hematology and Cancer Biology, Children's Hospital Medical Center,
University of Cincinnati, Cincinnati, OH 45229, USA

Abstract

A recent study shows that the pro-tumorigenic guanine nucleotide exchange factor Vav1 functions as a tumor suppressor in T-ALL through its ability to complex with Cbl-b ubiquitin ligase and intracellular domain of Notch1 (ICN1) and to promote ICN1 degradation. Vav1 can act as a double-edged sword in tumorigenesis.

Keywords

Vav1; Rho GEF; oncogene; tumor suppressor; Notch 1; T-ALL

Rho family GTPases (e.g. Rac1, RhoA, and Cdc42) are tightly regulated, molecular switches that cycle between GDP-bound inactive form and GTP-bound active form. The activation of Rho GTPases is mediated by guanine nucleotide exchange factors (GEFs) that catalyze the GDP/GTP exchange reaction, whereas the deactivation is accelerated by GTPase-activating proteins (GAPs) [1] (Figure 1A). Endowed with a broad spectrum of cellular functions including regulation of actin cytoskeletal organization, cell proliferation, survival, adhesion, and migration, Rho GTPases are known to be involved in tumorigenesis [1, 2]. Rho GEFs are considered pro-oncogenic, as many of them were first identified by virtue of their transforming capability in promoting foci-formation in fibroblasts [3] (Figure 1A). Vav1, a founding member of the Rho GEF family, activates Rac1 GTPase through its DH-PH domain module, and oncogenic activation of Vav1 occurs through phosphorylation or mutation of its N-terminal domain, which releases a self-inhibition of the DH domain, underlying an intramolecular regulatory mechanism [4] (Figure 1B). Vav1 is overexpressed in pancreatic cancer cells and contributes to pancreatic tumorigenesis [5]. Gain of function mutations of Vav1 have also been detected in adult T cell leukemia/lymphoma, peripheral T-cell lymphomas and lung adenocarcinoma [6, 7].

In a recent issue of *Cancer Cell*, Robles-Valero *et al.* report that Vav1 functions as a tumor suppressor in T-cell acute lymphoblastic leukemia (T-ALL) [8], a type of cancer that arises from the malignant transformation of immature T lymphocyte progenitors. The authors studied tumor development in carcinogen (e.g. DMBA)-treated mice bearing a genetic

*To whom correspondence should be addressed. Yi.zheng@cchmc.org. Phone: 513-636-0595. Fax: 513-636-3768.

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deletion of Vav1. Vav1^{-/-} mice developed tumors more rapidly and with higher frequencies of cancerous cells characteristic of immature T cells, compared to carcinogen-exposed wild-type (WT) mice. Mechanistically, Vav1^{-/-} T-ALL cells showed similar transcriptome to that of T-ALL cells derived from bone marrow precursors ectopically expressing ICN1, the cytoplasmic domain of Notch1 that is released from Notch1 through ADAM- and γ -secretase-mediated cleavage. ICN1 mediates gene transcription in immature T cells, which are essential for thymocyte and T-ALL development. Moreover, Vav1^{-/-} T-ALL cells shared a gene signature with preleukemic thymocyte populations depleted of Zfp3611 and Zfp3612 that are known to prevent T cell transformation through inhibition of Notch1 translation [9]. These data suggest that the loss of Vav1 might be related to an upregulated Notch1 pathway, leading to T-ALL development. Indeed, Vav1^{-/-} T-ALL cells upregulated the mRNA levels of Hes1, Myc, Notch1, and Notch3, and the protein level of ICN1, all of which are indicative of Notch1-driven T-ALL. Importantly, the increased Notch1 signaling was required for potentiating T-ALL in the Vav1 deficient mouse model. Vav1 deficiency also caused an elevation in ICN1 independent from the mutation status Notch1 or Fbxw7, the Notch1 E3 ubiquitin ligase, by inhibiting ICN1 ubiquitination and degradation but not by promoting Notch1 cleavage. Interestingly, a Vav1-mediated adaptor function through the two C-terminal SH3 domains, but not the GEF catalytic function or SH2 domain, is important for the modulation of ICN1 activity. Since Vav1 adaptor domains have been found to bind to Cbl-b, an E3 ubiquitin ligase [10], the authors further examined whether Cbl-b is involved in ICN1 degradation. Vav1, Cbl-b and ICN1 were bound to one another, and Cbl-b knockdown mimicked the Vav1 deficient phenotype and increased ICN1 abundance and reduced ICN1 ubiquitination, implicating Cbl-b in Vav1-dependent inhibition of ICN1 transcriptional activity. These biochemical and cell biological results demonstrate that Vav1 mediates ICN1 degradation and function through nucleation of an ubiquitination complex with Cbl-b and ICN1.

Subsequent *in silico* analyses of three molecularly defined subtypes of human T-ALL patient samples saw that TLX⁺ T-ALL patient cells contained reduced Vav1, a similar gene signature to the murine Vav1^{-/-} T-ALL cells, and increased ICN1 downstream target (i.e. Hes1). Ectopic expression of TLX in TLX⁻ T-ALL cells or knockdown of TLX in TLX⁺ T-ALL cells revealed a causal relationship of TLX with Vav1 downregulation and an increase in ICN1 protein level. Modulation of Vav1-Cbl-ICN1 by TLX underlies TLX⁺ T-ALL survival and proliferation, thus clearly demonstrating the clinical significance of a tumor suppressor role for the Vav1-Cbl-b-ICN1 complex in TLX⁺ T-ALL.

The discovery of a tumor suppressor role of Vav1 highlights the complex function of Rho GTPase regulators in tumor biology, and has multiple mechanistic and translational implications. Previous cell biology studies have established that most Rho GTPases and their positive regulators, i.e. Rho GEFs, are pro-oncogenic, whereas their negative regulators such as Rho GTPase activating proteins (GAPs) are anti-oncogenic (Figure 1A) [2]. However, recent genetic and genomic studies of animal models and human cancers have found that many Rho GTPases and Rho GEFs may have anti-tumorigenic activity, while certain Rho GAPs might promote oncogenesis [6]. For example, RhoA has recently been shown to inhibit K-Ras-induced hepatic adenoma formation, and loss-of-function RhoA mutations have been detected in angioimmunoblastic T cell lymphoma, peripheral T-cell lymphomas,

and Burkitt lymphoma [6]. The Rac GEF Tiam1 is found inhibitory in skin malignancies [6]. In this context, it is interesting that the tumor suppressor role of Vav1 in T-ALL does not rely on phosphorylation regulation and its catalytic GEF activity but is mediated through its SH3 adaptor domains in interacting with Cbl-b and ICN1 (Figure 1B). This is reminiscent of its adaptor function in the activation of NF-AT [7]; however, NF-AT activation by Vav1 adaptor function appears to favor the pathogenesis of peripheral T-cell lymphomas [7], whereas the tumor suppressor role of Vav1 appears to modulate immature T cell transformation leading to T-ALL. It is an important question whether non-catalytic functions of diverse adaptor domains seen in many Rho GEFs or GAPs may be involved in opposite cell growth/survival regulatory activity from that of the catalytic domains.

Another important issue to be further addressed is whether the nucleation function of Vav1 in forming an ubiquitination complex such as Vav1-Cbl-b-ICN1 may also have a tumor suppressor role in cancer types beyond T-ALL, particularly in other Notch-driven tumors [8]. Taking into account both the pro-oncogenic Rac1 GEF function and the tumor suppressor role of Vav1, rational targeting Vav1 for anti-cancer therapy needs to differentiate its catalytic vs. non-catalytic adaptor domains in defined cancer types in order to gain benefit from ablating such a double-edged sword.

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Figure 1. Role of Rho GTPases and Regulators Such as Vav1 in Tumorigenesis

(A) Rho GTPases cycle between a GDP-bound inactive form and a GTP-bound active form. GTP-loading is catalyzed by Rho guanine nucleotide exchange factors (Rho GEFs), whereas GTP-hydrolysis is facilitated by Rho GTPase-activating proteins (Rho GAPs). Rho GTPases are traditionally considered to be pro-tumorigenesis. (B) As a Rho GEF, Vav1 promotes tumorigenesis by activating Rac1 via its GEF catalytic domains (DH and PH), an effect dependent on tyrosine phosphorylation or mutations at its N-terminus. Vav1 can suppress tumorigenesis by nucleating the ubiquitin ligase Cbl-b and the intracellular domain of Notch1 (ICN1) via its C-terminal SH3 domains, leading to ubiquitination and degradation of ICN1 and reduced Notch signaling that is important for T-ALL development.