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Genes & Diseases

COMMENTARY

RhoA, a novel tumor suppressor or oncogene as a therapeutic target?☆

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Ras homolog gene family, member A (RhoA) is a small GTPase that plays critical roles in several essential cell functions, such as migration, adhesion, proliferation, and gene expression.[1] RhoA switches between a GTP-bound active form and a GDP-bound inactive form. The activated RhoA directly interacts with its downstream effectors, such as Rho kinase (ROCK) to regulate actomyosin dynamics, or mDia1 to control stress fiber and filopodia formation. The activity of RhoA is primarily regulated by guanine nucleotide exchange factors (GEFs), GTPase-activating protein (GAP), and guanine nucleotide-dissociation inhibitors (GDIs).

RhoA was initially postulated as an oncogene in 1989.[2] Even though the amplification of RhoA was capable of transforming mouse fibroblasts, point mutations at codon 14 and 64 were not tumorigenic in the same model.[2] Previous cancer genome sequencing analysis also failed to identify RhoA mutations in most common human cancers, and consequently, it was not thought to be altered by somatic mutation in human cancers. In February of 2014, a recurrent mutation of RhoA (G17V) was reported to be present in 67% of angioimmunoblastic T cell lymphoma (AITL) and 18% of peripheral T cell lymphoma (PTCL), but not otherwise specified (PTCL-NOS) samples.[3] This finding was quickly validated by two other groups.[4,5] In addition, RhoA mutations were found in pediatric Burkitt lymphoma

treated according to the NHL-BFM protocols.[6] However, RhoA mutation is not limited to a subset of lymphoma, as three large studies published this year have indicated that RhoA is mutated in 14% of diffuse-type gastric carcinoma samples but not in intestinal type tumors.[7—9] Therefore, RhoA is quickly emerging as a somatic mutational target in these tumor types.

The first interesting aspect of this emerging story is that RhoA mutations are limited to these specific tumor types, which suggests that the function of RhoA may be cell type-specific. It is known that the expression of many RhoA regulators is tissue or cell type-specific, and recent mouse model studies have indicated that the regulation of these downstream signaling pathways by RhoA is also cell type-specific.[10] Consequently, the biological significance of RhoA activity will vary among different cell types, and it will be important to determine in the future the biological effect of RhoA depletion in these cell types in mouse models.

The type of recurrent RhoA mutations observed in these tumors is another topic of interest. In AITL and PTCL, the dominant mutation observed is G17V, which resides in the GTP/GDP binding site. G17V-mutant RhoA does not interact with its effector molecule rhotekin and suppresses F-actin stress fiber formation.[3] In addition, G17V-mutant RhoA appears to act in a dominant-negative capacity to promote cell proliferation and invasion.[4] The mutational hotspots of RhoA in diffuse-type gastric carcinoma are Y42C, R5Q/W, L57V and G17E. Y42C resides at the C-terminal edge of the core effector binding region of RhoA, and a previous study suggested that this mutation only attenuates the activation of protein kinase N but does not abrogate the activation of mDia or ROCK1.[8] A Rho binding domain assay also suggested that Y42C and L57V mutants have attenuated abilities to associate with GTP.[9] Together, these studies suggest that wild-type RhoA has tumor suppressor functions, while mutated RhoA inhibits wild-type function through a dominant negative mechanism. However, if RhoA is truly a tumor suppressor, one would expect this gene to be frequently inactivated by other gene inactivation

mechanisms, such as nonsense or frame-shift mutations in these tumor types. The recurrent nature of RhoA mutations in AITL, PTCL and diffuse-type gastric carcinoma strongly suggests that these hotspot mutations result in a gain-of-function alteration in an unidentified signaling pathway; nevertheless, in the absence of any supporting data, the question still remains whether RhoA is an oncogene or tumor suppressor gene.

From the cancer treatment perspective, the recurrent mutational hotspots of this protein represent ideal targets for small molecule inhibitors as therapeutic reagents. If the RhoA mutants act in a dominant negative fashion, such molecules could disrupt their interaction with the wild-type protein to restore RhoA function. On the other hand, if RhoA mutants are oncogenes, the suppression of their activities by these molecules should inhibit tumorigenesis. In either case, the future development of these therapeutic reagents holds promise for cancer patients with RhoA mutations.

Acknowledgments

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Melissa Gilbert-Ross
Adam I. Marcus
Wei Zhou*
The Winship Cancer Institute, Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA 30322, USA

*Corresponding author.
E-mail address: wzhou2@emory.edu (W. Zhou)*

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