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RACK1 promotes the proliferation of THP1 acute myeloid leukemia cells

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Abstract The receptor for activated C kinase 1 (RACK1), an adaptor protein implicated in the regulation of multiple signaling pathways, has been reported to contribute to the survival of leukemic progenitor cells by enhancing the activity of glycogen synthase kinase 3β (GSK3β). However, it remains unknown whether RACK1 also contributes to the oncogenic growth of acute myeloid leukemia (AML) cells. Here, we report that transient or stable silencing of endogenous RACK1 expression by RACK1 short hairpin RNAs (shRNAs) led to impaired proliferation of THP1 AML cells without inducing terminal differentiation. Further exploration revealed that RACK1 loss-of-function resulted in reduced GSK3β activity. GSK3β shRNA treatment showed similar effects to RACK1 loss-of-function. Our data collectively suggest that RACK1 contributes to THP1 cell proliferation through, at least partially, enhancing GSK3β activity. Thus, targeting RACK1 may have some important therapeutic implications in the treatment of AML.

Keywords RACK1 · GSK3β · AML · Proliferation · Activity

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Introduction

Receptor for activated C kinase 1 (RACK1, 36 kDa), originally identified on the basis of its ability to anchor activated form of protein kinase C, is a highly conserved eukaryotic protein of the Trp-Asp 40 (WD40) superfamily [1, 2]. RACK1 is ubiquitously expressed and is now recognized as a multifunctional scaffold protein. Its peculiar β-propeller structure of seven WD40 repeats allows its interaction with multiple proteins in various signal-transduction pathways [1, 2].

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults. Long-term survival of patients with AML has changed little over the past decade despite of extensive studies. Thus, it is necessary to identify and validate new AML targets [3]. The glycogen synthase kinase 3β (GSK3β), a multifunctional serine/threonine (Ser/Thr) kinase, was originally discovered as a key enzyme in the control of glucose metabolism [3–5]. In addition, it was identified as a component of the Wnt signaling pathway, forming a complex with APC and Axin, which inactivates the pathway in the absence of Wnt ligands by phosphorylating and degrading β-catenin [3–5]. Even though the underlying mechanisms remain elusive, GSK3β has emerged as a target in hematological malignancies [3–5].

RACK1 plays a context-dependent role in tumorigenesis [6]. Recently, it has been revealed that RACK1 might contribute to the survival of leukemic progenitor cells by enhancing GSK3β activity [5]. However, it remains unknown whether RACK1 also contributes to the oncogenic growth of AML cells. Here, we report that transient or stable silencing of endogenous RACK1 expression by RACK1 short hairpin RNAs (shRNAs) led to impaired proliferation of THP1 AML cells without inducing