

# Rheb's role in cancer

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Two independent papers in the August 15th issue of *G&D* identify the Rheb GTPase as a novel oncogene and a promising new chemotherapeutic target.

The first paper, from Dr. Pier Paolo Pandolfi (BIDMC and Harvard Medical School) and colleagues, demonstrates that the Ras-like small GTPase, Rheb, is directly involved in prostate tumorigenesis.

Through the overexpression of Rheb specifically in prostate tissue of live mice, the researchers were able to show that increased Rheb signaling activity is sufficient to induce low-grade prostate neoplasias. Furthermore, in combination with decreased PTEN activity, Rheb overexpression can stimulate aggressive prostate tumor formation.

"The identification of Rheb as a gene involved in the pathogenesis of cancer opens new avenues for the development of anti-cancer therapies, as Rheb is an inherently 'druggable' target. Indeed, we are already testing such drugs alone, and in combination with other chemotherapeutics in faithful animal models," explains Dr. Pandolfi.

In the accompanying paper, Dr. Hans-Guido Wendel (Memorial Sloan Kettering Cancer Center) and colleagues present evidence that Rheb can also function as an oncogene in lymphomagenesis.

Using an experimental animal model of human lymphoma, the researchers demonstrated that Rheb overexpression contributes to lymphoma formation. They also pinpointed Rheb overexpression as a

naturally occurring genetic mutation in human patient-derived lymphoma tumor samples. In addition, Dr. Wendel and colleagues found that the targeted inhibition of Rheb can effectively counteract tumor progression in lymphomas with this unique genetic signature.

Dr. Wendel emphasizes that "The key clinical implication is that Rheb levels in tumor tissue could indicate patients that will benefit from relatively non-toxic therapies with targeted drugs like rapamycin or inhibitors of the farnesyltransferase enzyme."

Source: Cold Spring Harbor Laboratory

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