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NDRG2 plays a pivotal role in ATLL leukaemogenesis by regulating the PTEN-mediated PI3K/AKT signalling pathway

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Adult T-cell leukemia/lymphoma (ATLL) is a rare and aggressive T-cell leukemia/lymphoma that is etiologically linked to infection by human T-cell lymphotropic virus type 1 (HTLV-1). To find candidate causative genes for ATLL development, we used an integrative genomic analysis of ATLL and identified N-myc downstream-regulated gene 2 (NDRG2) as a candidate tumour suppressor gene on chromosome 14q11. Here we demonstrate that NDRG2 is a novel PTEN-interacting protein and recruits protein phosphatase 2A to facilitate the dephosphorylation of PTEN at the Ser380, Thr382, and Thr383 (STT) cluster within the C terminus. Although the PI3K/AKT signalling pathway is frequently activated in ATLL cells, neither the genetic alterations of the PTEN and PIK3CA genes nor the transcriptional down-regulation of PTEN expression were detected in ATLL. We found that activation of the PI3K/AKT signalling pathway in ATLL is mediated through hyperphosphorylation of PTEN-STT, a well-known mechanism of PTEN inactivation, by down-regulation of NDRG2 expression. Moreover, we found that NDRG2 deficiency in mice results in constitutive PI3K/AKT activation in various organs and high incidence of T-cell lymphoma and other types of cancer. Since down-regulation of NDRG2 expression via promoter methylation has been reported in various types of cancer, activation of the PI3K/AKT pathway by the enhanced PTEN-STT phosphorylation through the inactivation of NDRG2 is crucial for the development of a wide range of cancer cells including ATLL, which harbor no activating genetic alterations in the PI3K/AKT pathway.

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