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Progranulin deficiency increases vulnerability of human neuroblastoma SH-SY5Y cells to serum withdrawal-induced apoptosis

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Null mutations in GRN are associated with frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP). However the influence of progranulin (PGRN) deficiency on neurodegenation is largely unknown. In neuroblastoma cells, silencing of GRN gene causes significantly reduced cell survival after serum withdrawal. It was observed that PGRN deficient cells (KD GRN) are more vulnerable to serum deprivation than control cells. The supplementation of recombinant human PGRN restored the survival of KD cells. The following observations suggest that modulation of the CDK6/pRb pathway secondary to changes in the activity of the PI3K/Akt and ERK1/2 signaling pathways, induced by PGRN levels is involved in the altered regulation of serum deprivation-induced apoptosis. (i) The specific CDK6 inhibitors, sodium butyrate or PD332991 sensitized control SH-S5Y5 cells to serum deprivation-induced apoptosis without affecting survival of PGRN deficient cells. (ii) CDK6/pRb seems to be downstream of the PI3K/Aktand ERK1/2pathways since their specific inhibitor, Ly294002 and PD98059 were able to decrease CDK6 activity and induced death of control SH-SY5Y cells. (iii) PGRN deficient cells show reduced stimulation of Akt, ERK1/2, and CDK6-associated kinase activities than in control cells in the absence of serum. These observations highlight the important role of PGRN-mediated stimulation of the PI3K/Akt/ERK1/2 and CDK6/pRb pathways in determining the cell fate survival/death under serum deprivation.

Biography

Angeles Martin Requero is Doctor of Biological Sciences, Complutense University of Madrid in 1978. she completed Postdoctoral Fellow in University of Pennsylvania, Philadelphia, USA in 1979-1982. She worked as as a Professor in University of Extremadura (1982-1983). Scientific Holder in 1985. In 1996-1997 she worked as a Visiting Scientist in Medical Scholl, University of California (UCLA), Los Angeles, USA. In 2008 she is a Research Scientist.she currently heads the laboratory devoted to "study the cellular and molecular basis of Alzheimer's disease and other dementias, " in the Department of Cellular and Molecular Medicine, Center for Biological Research (CSIC). She has authored more than 50 publications in international journals and a hundred communications in national and international conferences.

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