IJAE
Vol. 119, n. 1 (Supplement): 88, 2014
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Phospholipase c beta 1 (PLCb1) in acute myeloid leukemia (AML): a novel potential therapeutic target

Roberta Fiume[1], Xu Huang[2], Giulia Ramazzotti[1], Sara Mongiorgi[1], Patrizia Santi[1], Tim Somervaille[2], Nullin Divecha[3]

[1] Università di Bologna – Dipartimento di Scienze Biomediche e Neuromotorie, Bologna, Italy
[2] Leukaemia Biology Laboratory, Cancer Research UK Manchester Institute, United Kingdom
[3] Centre for biological sciences, University of Southampton, United Kingdom

Acute myeloid leukemia (AML) is the most common type of leukemia in adults in which leukemic myeloid derived cells replace normal blood cells leading to a loss in systemic function. Once initiated the disease develops rapidly and is typically fatal within weeks or months if left untreated. AML is a complex disease and although, the exact causes of the development of AML are unknown, risk factors include age, pre-leukemic diseases such as myelodysplastic syndrome, exposure to chemicals and radiation and genetics. The mainstay treatment is still chemotherapy together with stem cell replacement therapy and while life expectancy has increased slowly, the 5 year survival rates range between 12 and 70% with relapse rates as high as 70% depending on the subtype (canceruk). These statistics illustrate the urgent requirement for the development of novel targeted therapeutics.

Phospholipases C (PLC) are critical intracellular signaling enzymes that control a wide range of cellular functions including proliferation and apoptosis that have been implicated in myelodysplastic diseases and in leukemia (Faenza et al., 2013; Shah et al.). Importantly they constitute a highly druggable family of enzymes distinct from other well established drug development targets such as protein kinases. Using the human leukemic cell line THP1, we carried out a small targeted RNAi screen to establish a role of all known PLCs in cell growth, differentiation and maintenance of the transformed phenotype. We discovered that silencing of PLCb1 or PLCH2 resulted in a strong growth arrest. PLCb1 knockdown also initiated apoptosis and attenuated growth of THP1 cells in semisolid culture, which is known to reflect the ability of cells to induce leukemia in vivo. Accordingly, we found that knockdown of PLCb1 strongly attenuated THP1-mediated development of leukemia in mice. These growth inhibitory effects of PLCb1 knockdown were extended to a mouse model of human leukaemia induced by the MLL-AF9 translocation and to human primary leukemia cells. Of direct importance to the consideration for drug development we observed that PLCb1 knockdown selectively attenuated the growth of primary human AML cells, without effecting cell growth and differentiation of normal $CD34^+$ hematopoietic stem and progenitor cells from healthy donors. We therefore propose PLCb1 as a novel candidate for a therapeutic target in AML.

References

canceruk: www.cancerresearchuk.org/
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