THROMBOPOIETIN (TPO) INDUCES C-MYC EXPRESSION THROUGH A PI3K-DEPENDENT PATHWAY THAT IS NOT MEDIATED BY AKT, PKC_ζ OR MTOR IN TPO-DEPENDENT CELL LINES AND PRIMARY MEGAKARYOCYTES

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ธรรมบอยฟอยซิน (Thrombopoietin) ขึ้นไปการแสดงออกของ c-myc (c-myc) ผ่านทางวิถีที่ต้องพ่อโฟรโฟริโอซินของ 3 ไนเซส (PI3-K) ซึ่งไม่ต้อง โปรดินไนเซส ปี (AKT), โปรดินไนเซสซี เขต (PKCζ) หรือ เป็นหมายเลขของร่างกายชั้น (mTOR) เป็นสัญญาณทางในเซลล์ที่ต้อง พึง(IBM-โฟรโฟริโอซิน) และใน แมกแกรียริโอซิน (megakaryocyte) (THROMBOPOIETIN (TPO) INDUCES C-MYC EXPRESSION THROUGH A PI3K DEPENDENT PATHWAY THAT IS NOT MEDIATED BY AKT, PKCζ OR MTOR IN TPO-DEPENDENT CELL LINES AND PRIMARY MEGAKARYOCYTES)
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ABSTRACT

Thrombopoietin (TPO) and its receptor (c-Mpl) are the major regulator of megakaryocyte and platelet production and serve a critical and non-redundant role in hematopoietic stem cell (HSC) biology. TPO signals through the Jak-STAT, Ras-Raf-MAPK, and PI3K pathways, and promotes survival, proliferation, and polyploidization in megakaryocytes. The proto-oncogene c-myc also plays an important role in many of these same processes. In this work we studied the TPO regulated expression of c-myc in TPO-dependent cell lines and primary megakaryocytes by quantitative real-time RT-PCR. We found that TPO induced expression of c-myc in 1 hour in both hematopoietic cell lines (UT-7 and BaF3/Mpl) and mature murine megakaryocytes. The TPO-induced expression of c-myc was blocked by a phosphatidylinositol 3-kinase (PI3K) inhibitor, suggesting that TPO stimulated c-myc expression through a PI3K-dependent pathway. Of interest, our study showed that overexpression of active Akt did not rescue the effect of PI3K blockade on c-myc expression, rather, enhancing it. In addition, inhibitors of protein kinase C (PKCζ) and the target of rapamycin (mTOR) also failed to affect c-myc mRNA expression, while c-myc mRNA expression was reduced by inhibition of the mitogen activated protein kinase (MAPK) pathway. Therefore, we conclude that TPO stimulates c-myc expression in primary megakaryocytes through a PI3K- and MAPK-dependent pathway that is not mediated by Akt, PKCζ or mTOR.

KEY WORDS: THROMBOPOIETIN/ C-MYC/ MEGAKARYOCYTE/ PI3-K/ AKT/ PKCζ/ mTOR/ MAPK

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