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## Phthalates acting as a tumor promoter through nongenomic AhR/HDAC6/c-Myc signaling in ER negative human breast cancer

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The environmental hormone phthalates play important roles in regulating the expression of genes involved in cell proliferation, drug resistance, and breast cancer risk. However, their precise mechanism in tumor progression in breast cancer remains unclear. To elucidate the effect of phthalates on tumor progression, we evaluated the consequences of phthalate treatment on tumor growth and motility in breast cancer cells. We found that phthalates increased ER negative breast cancer cells growth, migration, invasion, colony formation, and stimulated tumor growth in nude mice. In addition, phthalates are mediators of non-genomic actions of AhR at the plasma membrane and increased HDAC6 expression in MDA-MB-231 cells. Phthalate treatment induced non-genomic signals of AhR through cyclic AMP/PKA activation at Ser133 of CREB1 and permitted CREB1 binding to the *HDAC6* promoter. Furthermore, a small interfering RNA targeting HDAC6 mRNA reduced  $\beta$ -catenin translocation to the nucleus and decreased c-Myc expression, resulting in the inhibition of proliferation and motility. Thus, the results identify a new pathway of AhR/HDAC6/c-Myc-mediated tumor-progression activity via exposure to phthalates in the ER negative breast cancer.