Background Lysine lactylation (Klac) is a novel post-translational modification that regulates pathology progression in response to lactate stimulation. Histone Klac was identified recently in the transformation of M1-type to M2-type macrophage. Di(2-ethylhexyl)phthalate (DEHP), which is the most common plasticizer in manufacturing medical and consumer products, was reported to cause the tumor progression by modulating macrophage polarization and activation. The underlying mechanism of DEHP-regulated macrophage polarization in promoting tumor progression remains unknown, thus driving us to decipher whether this regulation links to histone lysine lactylation in macrophages.

Methods 12-O-tetradecanoylphorbol-13-acetate (TPA) and interleukin 4 (IL4) were used to induced M0- and M2-type macrophage polarization from monocyte THP-1 cells. The impacts of DEHP on macrophage polarization and tumor cell viability in were analyzed in flow cytometry with specific markers for M1 and M2-type macrophage and apoptosis, respectively. We also disclosed the effect of DEHP on histone lactylation during macrophage polarization in Western blot analysis. The involved transcription factor and signaling pathways were identified by using various molecular biological analyses.

Results Our results showed that the DEHP-treated mouse group revealed high M2-type macrophage infiltration and IL-10 and TGFβ expressions in breast cancer tissues compared to those without DEHP treatment. In In vitro model, DEHP accelerated the glycolytic pathway and lactate production accompanied by the enhanced level of pan-Klac and histone lactylation (H3K18la) in M2-type macrophages. DEHP-derived pan-Klac was reversed by lactate dehydrogenase A (LDHA) inhibitor treatment. Moreover, DEHP also increased the expression of ESR1 and subsequently its interaction with lysine lactyltransferase p300, contributing to the transcriptional expressions of markers for M2-type macrophage. Knockdown of ESR1 decreased DEHP-conferred pan-Klac and the markers of M2-type macrophage. Interestingly, high expression of ESR1 was positively correlated with the infiltration of M2-type macrophage in breast cancer, not that of monocyte and M1-type macrophage. Taken together, these data demonstrated that DEHP induces the phenotype of polarized M2 macrophage via the ESR1-p300 axis-mediated histone lactylation, leading to the ability of tumor proliferation.

Conclusions Our results indicated that exposure to DEHP could hasten the infiltration of M2-type macrophages in the tumor microenvironment by upregulating histone lactylation. ESR1 could be a potential target to modulate the depolarization of macrophage.

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