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GPR30介导雌激素对三阴性乳腺癌MDA-MB-468细胞系增殖的作用

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Title: Effects of estrogen on GPR30-mediated proliferation in triple-negative breast cancer cell line MDA-MB-468

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关键词：GPR30；雌激素；三阴性乳腺癌；细胞增殖

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摘要：目的　探讨雌激素受体GPR30（或称G蛋白偶联雌激素受体G protein-coupled estrogen receptor，GPER）介导雌激素对三阴性乳腺癌细胞系MDA-MB-468增殖的影响。　方法　免疫荧光法及Western blot法检测MDA-MB-468细胞中受体GPR30的定位及表达量，流式细胞术及CCK-8法检测药物处理后的细胞周期和细胞生长变化，Western blot法检测磷酸化细胞外信号调节激酶（phospho-extracellular regulate kinase，p-ERK）以及周期蛋白CyclinD1的蛋白表达。　结果　雌激素受体GPR30在MDA-MB-468细胞中高表达，且主要表达于细胞质。17-β雌二醇（E_2）、GPR30特异性激动剂（G1）与他莫昔芬（TAM）处理细胞后，均显著促进细胞周期进展和细胞增殖。其中处于DNA合成期（S期）的DNA量分别为空白对照组的（2.81±0.11）、（2.82±0.21）、（2.70±0.20）倍，相对细胞数分别为空白对照组的（1.83±0.18）、（1.94±0.12）、（1.92±0.16）倍，其促生长效应被GPR30特异性拮抗剂（G15）显著抑制（$P<0.05$）。E_2、G1及TAM处理组中p-ERK及CyclinD1的蛋白相对表达量分别是空白对

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照组的（2.59±0.21）、（2.43±0.25）、（2.26±0.34）倍以及（1.67±0.06）、（1.51±0.08）、（1.90±0.07）倍，G15可抑制E_2、G1及TAM所引发的相应变化（*P*<0.05）。　　结论　　雌激素活化GPR30刺激下游ERK信号通路上调p-ERK及周期蛋白CyclinD1的表达，促进细胞周期的进展，导致三阴性乳腺癌细胞系MDA-MB-468异常增殖。

Abstract:　Objective　To explore the effects of estrogen on the proliferation of triple-negative breast cancer cell line MDA-MB-468 mediated by G protein-coupled estrogen receptor GPR30.　Methods　Fluorescence immunoassay and Western blotting were performed to examine the localization and expression of GPR30 in MDA-MB-468 cells. Cell cycle and cell proliferation were tested by flow cytometry and CCK-8 assay. The expression of phospho-extracellular regulate kinase (p-ERK) and Cyclin D1 was detected by Western blotting.　Results　GPR30 was detected with high expression level in the MDA-MB-468 cells and located mostly in the cytoplasm. After treatment with 17-β-estradiol (E_2), GPR30 specific agonist (G1) and tamoxifen (TAM), the progression of cell cycle and cell proliferation was increased remarkably. The DNA contents in DNA synthesis (S) phase were 2.81±0.11, 2.82±0.21, and 2.70±0.20 times higher and the relative cell numbers were 1.83±0.18, 1.94±0.12, and 1.92±0.16 times higher than those of the control group, respectively. The above effects induced by E_2, G1 and TAM could be blocked by GPR30 specific antagonist G15 (*P*<0.05). The relative protein level of p-ERK in the E_2, G1 and TAM treatment groups was 2.59±0.21, 2.43±0.25, and 2.26±0.34 times higher and that of cyclin D1 was 1.67±0.06, 1.51±0.08, 1.90±0.07 times higher than those of the control group, respectively (*P*<0.05). Interestingly, the changes induced by E_2, G1 and TAM were inhibited by G15 (*P*<0.05).　Conclusion　Estrogen triggers downstream ERK signaling by activating GPR30 to up-regulate the expression of p-ERK and cyclin D1, which accelerates MDA-MB-468 cell cycle progression, leading to abnormal cell proliferation.

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