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表皮生长因子影响人羊膜间充质干细胞迁移的机制

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Effect of Epidermal Growth Factor on Migration of Human Amniotic Mesenchymal Stem Cells

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摘要 目的研究表皮生长因子（EGF）影响体外培养的人羊膜间充质干细胞（hAMSCs）迁移的机制。 **方法** 将体外培养的hAMSCs分为对照组（未处理）、EGF组、抑制剂AG1478+EGF组、抑制剂LY294002+EGF组和抑制剂U0126+EGF组5组，采用Transwell小室测定各组hAMSCs的迁移能力，Western blot检测各组磷酸化EGFR（P-EGFR）、磷酸化AKT（P-AKT）和磷酸化ERK1/2（P-ERK1/2）及金属蛋白酶（MMP）-2和MMP-9的表达情况，RNA-Seq 技术对EGF组和对照组细胞中差异表达基因进行分析。 **结果** EGF组细胞的迁移能力明显高于对照组（*P*=0.0361），抑制剂AG1478+EGF组（*P*=0.0113）、抑制剂LY294002+EGF组（*P*=0.0169）和抑制剂U0126+EGF组（*P*=0.0293）明显低于EGF组。EGF可增加hAMSCs的P-EGFR、P-AKT和P-ERK1/2及MMP-2的表达，但P-AKT和P-ERK表达的增加可被AG1478和LY294002 抑制。对EGF组和对照组细胞中差异表达基因的 GO 功能富集分析和 KEGG代谢途径分析结果表明，EGF组细胞中发生转录上调的基因主要参与转录调节、蛋白质修饰、凋亡抑制等生命过程，其中与MAPK信号通路有关的基因为DUSP5、IL1B、DUSP6、NGF和HSPA2。 **结论** EGF引起的hAMSCs迁移可能是通过PI3K/AKT、ERK信号通路介导的，需要MMP-2的表达，及其参与转录调节、蛋白质修饰和凋亡抑制等基因的协同表达。

关键词： 人羊膜间充质干细胞 表皮生长因子 磷脂酰肌醇激酶-3 细胞外调节蛋白激酶

Abstract： Objective To explore the mechanism via which the epidermal growth factor (EGF) affects the migration of human amnion-derived mesenchymal stem cells (hAMSCs). Methods*In vitro* cultured hAMSCs were divided into control (untreated), EGF group, inhibitor AG1478+EGF group, inhibitor LY294002+EGF group, and inhibitor U0126+EGF group. The migration ability of hAMSCs in each group was measured using Transwell chamber. The expressions of phosphorylated EGFR (P-EGFR), phosphorylated AKT(P-AKT), and phosphorylated ERK1/2(P-ERK1/2) as well as the expressions of metalloproteinase (MMP)-2 and MMP-9 were detected using Western blot analysis. The differentially expressed genes in the culture solutions in EGF groups and control group were analyzed with RNA-Seq technique. ResultsCells in EGF group had significantly stronger migration ability than in control group (*P*=0.0361), inhibitor AG1478+EGF group (*P*=0.0113), inhibitor LY294002+EGF group (*P*=0.0169), and inhibitor U0126+EGF group (*P*=0.0293). EGF increased the phosphorylation levels of EGFR, AKT and ERK, and increased the expression of MMP-2. However, the increased expressions of P-AKT and P-ERK could be suppressed by AG1478 and LY294002. As shown by GO functional enrichment analysis and KEGG pathway analysis, EGF increased the transcription of genes, which were mainly involved in transcriptional regulation, protein modification, and apoptosis inhibition. Genes that were involved in the MARK pathway included DUSP5, IL1B, DUSP6, NGF, and HSPA2. ConclusionEGF-induced migration of hAMSCs may be mediated by the signaling pathways of PI3K and ERK, which needs MMP-2 expression and the co-expression of genes involved in transcriptional regulation, protein modification, and apoptosis inhibition.

Keywords： human amniotic mesenchymal stem cells epidermal growth factor phosphatidylinositol 3-kinases extracellular regulated protein kinases

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