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本期目录/Table of Contents
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低氧诱导因子-1α对骨形态发生蛋白2诱导的干细胞成软骨、成骨分化的影响

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Title: HIF-1α potentiates BMP2-induced chondrogenic differentiation but inhibits osteogenic differentiation in stem cells

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摘要: 目的 探讨低氧通路中关键转录调控因子低氧诱导因子-1α（hypoxia inducible factor -1α，HIF-1α）对骨形态发生蛋白2（bone morpho-genetic protein 2，BMP2）诱导干细胞骨、软骨分化的影响，阐明HIF-1α在干细胞成骨、软骨分化中的作用。方法 构建相应腺病毒AdBMP2、AdHIF-1α、AdGFP,单独或共同感染干细胞，Western blot法检测成软骨、成骨分化关键转录调控因子Sox9、Runx2的表达，Real-time PCR法检测成软骨、成骨分化标志物COL2A1、aggrecan、COL1A1和ALP mRNA表达，Alcian blue、ALP及Alizarin red S 染色检测软骨细胞外基质及骨基质钙盐沉积情况。进行干细胞裸鼠皮下移植，观察不同处理组形成骨块的组织结构情况，探讨HIF-1α对BMP2诱导干细胞成骨、软骨分化的影响。 结果 诱导分化后第1、3天，BMP2+HIF-1α组Sox9蛋白表达明显高于BMP2单独处理组，而BMP2+HIF-1α组Runx2蛋白

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表达明显低于BMP2单独处理组。诱导分化后第7、9天，BMP2+HIF-1α组COL2A1、aggrecan mRNA相对表达明显高于BMP2单独处理组（$P<0.05$），而BMP2+HIF-1α组COL1A1、ALP mRNA相对表达明显低于BMP2单独处理组（$P<0.05$）。Alcian blue染色发现BMP2+HIF-1α组软骨细胞外基质分泌多于BMP2单独处理组，染色更深；ALP染色发现BMP2+HIF-1α组ALP的活性弱于BMP2单独处理组；茜素红染色发现BMP2+HIF-1α组较BMP2单独处理组骨基质钙盐沉积更少；体内试验组织学观察见BMP2+HIF-1α组软骨成分更多，骨化不明显，BMP2单独处理组软骨成分少，软骨内骨化更明显。　　结论　　HIF-1α明显增强了BMP2诱导的干细胞成软骨分化，抑制了成骨分化及软骨内骨化，维持了软骨分化表型。

Abstract:　　Objective　　To determine the effect of hypoxia inducible factor-1α (HIF-1α) on bone morphogenetic protein 2 (BMP2)-induced chondrogenic and osteogenic differentiation in stem cells.　　Methods　　Recombinant adenoviruses AdBMP2, AdHIF-1α and AdGFP were generated to transfect mouse stem cell line C3H10T1/2. We detected the protein levels of Sox9 and Runx2 (chondrogenic and osteogenic differentiation critical regulatory factors) by Western blotting and the mRNA levels of COL2A1, aggrecan, COL1A1 and ALP (chondrogenic and osteogenic differentiation markers) by real-time PCR. Alcian blue staining, ALP staining and Alizarin red S staining were used to detect the secretion of cartilaginous matrix, ALP activity and bone matrix mineralization, respectively. We further demonstrated the role of HIF-1α in BMP2-induced chondrogenic and osteogenic differentiation by subcutaneous stem cell implantation in nude mice.　　Results　　On day 1 and day 3, the BMP2+HIF-1α group (stem cells treated with AdBMP2 and AdHIF-1α) showed significantly higher protein level of Sox9 and significantly lower protein level of Runx2 than the BMP2 group (stem cells treated with AdBMP2). On day 7 and day 9, the BMP2+HIF-1α group showed significantly higher mRNA level of COL2A1 and aggrecan ($P<0.05$) and significantly lower mRNA levels of COL1A1 and ALP ($P<0.05$) than the BMP2 group. We also found that the secretion of cartilaginous matrix in the BMP2+HIF-1α group was more than that in the BMP2 group, proven by Alcian blue staining. Bone matrix mineralization was not obvious in the BMP2+HIF-1α group as compared to the BMP2 group.　*In vivo*, the BMP2+HIF-1α group formed more cartilage structures, but the BMP2 group formed more bone structures.　　Conclusion　　HIF-1α promotes BMP2-induced stem cell chondrogenic differentiation but inhibits osteogenic differentiation and endochondral ossification and maintains chondrogenic phenotype.

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