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论著

南蛇藤素和扁蒴藤素显著下调HLA-B*2705启动子的活性

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摘要 目的： 利用高通量药物筛选方式，为寻找潜在的脊柱关节炎（SpA）新的治疗药物提供理论依据。方法：选取12 264小分子化合物分别使用293T-HLA-B27和 HeLa- HLA-B27稳定细胞株，观察对HLA- B*2705启动子有调节作用的化合物，筛选能够下调HLA-B*2705启动子活性的阳性化合物：启动子活性>150%为激动剂，启动子活性<60%为抑制剂。并且对进一步筛选出的抑制剂进行细胞毒性试验及半数抑制浓度/半数效应浓度（IC50/ EC50）检测，筛选出具有较好剂量一效应的阳性化合物。结果：(1)使用293T-HLA-B27细胞第1次筛选出624种阳性化合物，阳性率为5.1%； (2)使用HeLa-HLA-B27细胞株对上述624种化合物进行再次筛选，有70种化合物再次显示出对B*2705启动子活性的增强或者抑制作用；(3)进行EC50/IC50检测的40种化合物中，6种化合物为抑制剂，表现出较好的剂量一效应曲线，其中南蛇藤素和扁蒴藤素均为雷公藤类衍生物。结论：南蛇藤素和扁蒴藤素可下调HLA-B27表达，提示在今后针对HLA-B*2705相关的SpA患者治疗中，它们可能是值得研究的潜在有效化合物。

关键词 HLA-B*2705启动子； 雷公藤属； 脊椎关节炎

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Caelastrol and pristimerin derived from Leigongteng inhibit promoter activity of HLA-B*2705 gene

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Abstract

<FONT face=Verdana>AIM: To screen the effective chemicals, which can suppress the promoter activity of the HLA-B*2705 gene as potential therapeutic agents. METHODS: The HeLa-HLA-B27, 293T-HLA-B27 stable transfectants were used to monitor the effect of 12 264 chemicals through high throughput screening (HTS). Chemicals which regulates HLA-B*2705 promoter activity more than 150% or less than 60% were picked out for the further IC50/EC50 and cell viability detection. RESULTS: (1) The primary screening used by 293T-HLA-B27 stable transfectant yielded about 5.1% hits which either suppressed (556 chemicals) or enhanced (68 chemicals) the HLA-B*2705 promoter activity. (2) A reconfirmation screening was carried out with these 624 of the candidates using transfected HeLa-HLA-B27 cells. Seventy hits were confirmed. (3) Based on the bioinformatics of those positive hits, 40 chemicals were selected for in-depth analysis by dose-response experiment and IC50/EC50 detection. Six suppressors showed potential pharmacological activities. Interestingly, two suppressors (celastrol and pristimerin) are derived from Leigongteng, a herbal medicine already used for several decades for treatment of immune regulatory and inflammatory diseases. Four active chemicals were computer designed with no relevance to the above structures. CONCLUSION: Chinese traditional herb Nansheteng and Leigongteng might be the potential drugs for HLA-B27 positive patients. These results provide new direction for research in both the therapeutics and the pathogenesis of spondyloarthritis.</FONT>

Key words HLA-B*2705 promoter Tripterygium Spondyloarthritis

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