

HYDROXYCHLOROQUINE POTENTIATES THE FAS-MEDIATED APOPTOSIS OF RHEUMATOID SYNOVIOCYTES BY DOWNREGULATING FLICE-INHIBITORY PROTEIN EXPRESSION

The Catholic University of Korea, Center for Rheumatic Diseases; Seung-Jae Hong*, So-Youn Min, Mi-La Cho, Jin-Jung Choi, Kyung-Soo Park, Jong-Hyun Yoon, Do-June Min, Wan-Uk Kim, Jun-Ki Min, Sung-Hwan Park, Chul-Soo Cho, Ho-Youn Kim.

OBJECTIVE: Hydroxychloroquine (HCQ) is commonly used drug in the treatment of rheumatoid arthritis (RA) and has been reported to modulate the apoptosis of T cells. Inadequate apoptosis is considered to contribute to hyperplasia of synovial tissues and overexpression of FLICE-inhibitory protein (FLIP), apoptotic inhibitor, is known to be implicated in resistance to Fas-mediated apoptosis of synovial cells. In this study, we investigated whether HCQ induces the apoptosis of rheumatoid synoviocytes, and modulates the expression of FLIP. **METHODS:** Fibroblast-like synoviocytes (FLS) were prepared from the synovial tissues of RA patients and cultured with varying concentration of HCQ (1-100 mM) in the presence or absence of agonistic anti-Fas antibody (CH11). The apoptosis was measured using a cellular DNA fragmentation ELISA and the expression of FLIP was examined by Western blot and RT-PCR analysis. **RESULTS:** Treatment with HCQ ranging from 1 to 100 mM induced the apoptosis of FLS in a dose-dependent manner. The apoptosis induced by 50 ng/ml of anti-Fas antibody was comparable to that by 10 mM of HCQ. Combined treatment of HCQ (10 mM) and anti-Fas antibody (50 ng/ml) synergistically enhanced the apoptosis of FLS compared to either anti-Fas antibody or HCQ alone. The level of FLIP was found to be highly expressed in unstimulated FLS and rapidly decreased by HCQ treatment. The reduction of FLIP expression by HCQ was dose-dependent, and was observed in both protein and mRNA levels. Furthermore, decreased expression of FLIP by HCQ preceded apoptosis induced by HCQ plus anti-Fas antibody. **CONCLUSION:** These data suggest that HCQ sensitizes the Fas-mediated apoptosis of rheumatoid synoviocytes by downregulating FLIP expression, and the suppression of FLIP by HCQ may account for in part its beneficial effect in RA.

성인형 스틸씨병 환자들의 임상적 특성 및 싸이토카인의 측정

아주대병원 알레르기-면역내과

최정희*, 이영목, 서유진, 남동호, 박해심

배경 및 목적: 성인형 스틸씨병은 전신형의 소아 류마티스 관절염(스틸씨병)과 동일한 형태의 임상상을 가지는 질환으로 아직까지 그 원인이나 병인기전은 알려지지 않았다. 연구자들은 혈청 싸이토카인을 측정하여, 성인형 스틸씨병의 병인기전을 이해하고, 치료에 따른 질병의 활성도를 추적하기 위한 표지자로서의 활용성을 판정하고자 하였다.

방법: 1998년 2월부터 2001년 8월까지 아주대병원에서 Yamaguchi 등의 진단기준에 따라 성인형 스틸씨병으로 진단받은 17명을 대상으로 하였다. 임상적 소견 및 검사실 소견을 분석하였으며, 활성기와 치료후 비활성기의 혈청내 싸이토카인(sIL-2R, IL-6, INF- γ , IL-18)치를 면역효소법으로 측정하였다.

결과: 활성기 혈청에서 sIL-2R, INF- γ 가 정상치보다 증가되었으며($p > 0.05$), IL-18은 활성기와 비활성기 혈청 모두에서 정상치보다 유의하게 증가하였다($p < 0.01$), sIL-2R은 치료후 비활성기 혈청에서 유의하게 감소하였으나($p < 0.05$), INF- γ 와 IL-18은 치료전후의 유의한 차이는 없었다($p > 0.05$). sIL-2R은 혈청 ferritin, INF- γ , IL-18와 유의한 상관관계를 보였다($p < 0.05$). 진단당시 EBV 감염을 동반한 환자군($n=5$)이 EBV 감염을 동반하지 않은 환자군($n=9$)에 비해서 싸이토카인치의 유의한 차이는 없었으나($p > 0.05$), 혈청 ferritin치는 유의하게 낮았다($p < 0.05$).

결론: 성인형 스틸씨병은 활성화된 T 임파구와 IL-18이 병인기전에 관여할 것으로 생각되며, sIL-2R은 치료에 따른 질병의 활성도를 평가하는 표지자로 이용할 수 있다.