THERAPY

Resistance to adalimumab: is it predictable?

Gene expression profiling could be a useful method for identifying markers predictive of response to tumor necrosis factor (TNF) blockade in patients with rheumatoid arthritis (RA), according to the results of a study by Bernard Lauwerys and colleagues. The results have potential implications for clinical decision-making, and might also shed light on the pathways targeted by anti-TNF therapy.

In the study, synovial biopsy samples were obtained from 25 patients with active RA, despite therapy with DMARDs, at baseline and after 12 weeks of therapy with adalimumab. According to European League Against Rheumatism response criteria, 20 patients showed a good or moderate response to therapy, whereas 5 showed a poor response, a difference that was not accounted for by the patients' baseline clinical characteristics. The investigators first confirmed that adalimumab therapy induced substantial

changes in synovial cell populations in all patients, in particular reduced numbers of CD68⁺ cells. Global gene expression profiles identified 632 genes that were differentially expressed before and after treatment. Of note, pathway analyses indicated that a substantial percentage of these genes formed two major groups: genes involved in cell proliferation and genes involved in the regulation of immune responses. "Both pathways are known to have important roles in the RA synovium, and to be TNF-dependent," notes Lauwerys. "Our study demonstrates for the first time that they are major targets of TNF-blocking therapy in RA."

A comparison of pre-treatment gene expression profiles revealed that genes overexpressed at baseline in nonresponders clustered in the same general pathways, showing a correlation between clinical responses and gene signatures. Synovial levels of molecules representative of these gene groups were higher in nonresponders than in responders. "Interestingly," says Lauwerys, "we found that these genes could be induced *in vitro* in synovial fibroblast cell cultures after exposure to TNF, interleukin (IL)-1 β and, with greater effect, combinations of TNF and IL-1 β or TNF and IL-17." The results suggest that these cytokines could have a role in the mechanisms of resistance to anti-TNF therapy in patients with RA.

Sarah Price

Original article Badot, V. *et al.* Gene expression profiling in the synovium identifies a predictive signature of absence of response to adalimumab therapy in rheumatoid arthritis. *Arthritis Res. Ther.* 11, R57 (2009).