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Role of IL-1b in NLRP12-associated autoinflammatory disorders and resistance to anti-IL-1 therapy

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Background

A new class of autoinflammatory syndromes called *NLRP12*-associated disorders (NLRP12AD) has been associated with mutations in *NLRP12*. Conflicting data on the putative role of NLRP12 in IL-1b signaling have been generated *in vitro*.

Aim

This prospective study was undertaken to assess the secretion of IL-1b and three IL-1b-induced cytokines (IL-1Ra, IL-6 and TNF-a) in patients' PBMC cultured *ex vivo* and to evaluate the patients' response to recombinant IL-1 receptor antagonist (IL-1Ra, anakinra), a major drug in the treatment of autoinflammatory disorders.

Methods

Patients' disease manifestations and cytokine measurements were recorded before anakinra treatment was started, during 14 months of therapy, and after discontinuation of anakinra treatment.

Results

Spontaneous secretion of IL-1b by patients' PBMC was found to be dramatically increased (80 to 175-fold) compared to controls. Consistently, anakinra initially led to a marked clinical improvement and to a rapid near-normalization of IL-1b secretion. However, a progressive clinical relapse occurred secondarily, associated with an increase in TNF-a secretion, persistent elevated levels of IL-1Ra and IL-6 and a reactivation of IL-1b secretion. Anakinra was discontinued after 14 months of therapy.

Conclusion

Our findings provide *in vivo* evidence of the crucial role of IL-1b in the pathophysiology of NLRP12AD. This is the first time anakinra has been used to treat this disorder. This study provides new insights into the mechanisms underlying resistance to anti–IL-1 therapy observed in few patients with autoinflammatory syndromes. Our data also point to the potential interest of cytokine *ex vivo* measurements as predictors of response to treatment.

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