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# A cd8 alpha-negative subset of cd4+slamf7+ cytotoxic t cells is expanded in patients with igg4-related disease and decreases following glucocorticoid treatment

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**Background:** IgG4-Related Disease (IgG4-RD) is a fibro-inflammatory disorder characterised by tumefactive lesions, frequent elevation of serum IgG4 levels, and tissue fibrosis.[1] Glucocorticoids represent the treatment of choice to induce IgG4-RD remission but their effect on the cells orchestrating the disease remains unknown.[1] We recently describerd an unconventional population of clonally expanded $CD4^+SLAMF7^+$ cytotoxic T effector memory ($T_{EM}$) cells ($CD4^+$CTLs) and causally linked it to IgG4-RD in view of their capacity to secrete pro-fibrotic molecules and to infiltrate affected organs.[2–4]

**Objectives:** In order to better clarify the mechanisms of action of glucocorticoids in IgG4-RD and the pathogenic relevance of $CD4^+$ CTLs, we herein aim to describe the effects of corticosteroid treatment on $CD4^+$ CTLs.

**Methods:** CD8α, granzyme A, perforin, and SLAMF7 expression within the effector/memory compartment of CD45RO ($T_{EM}$) and CD45RA ($T_{EMRA}$) $CD4^+$ T cells was quantified by flow cytometry in 18 active IgG4-RD patients at baseline and after 6 months of glucocorticoid treatment. Eighteen healthy subjects were studied as controls. Next-generation sequencing of the T-cell receptor α and β

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d on circulating CD4$^+$CTLs in patients with treatment, and in affected tissues.

$^-$ $T_{EM}$ and $T_{EMRA}$ cells were not expanded ›ared to healthy controls. CD4$^+$SLAMF7$^+$ $T_{EM}$ cells (but not $T_{EMRA}$ cells) were significantly increased among IgG4-RD patients. Within CD4$^+$SLAMF7$^+$ $T_{EM}$ cells, CD8α$^-$ but not CD8α$^{low}$ cells were elevated in IgG4-RD patients. The same dominant clones of CD8α$^-$CD4$^+$SLAMF7$^+$ $T_{EM}$ cells found in the peripheral blood were also identified in affected tissue. Both CD8α$^-$ and CD8α$^{low}$ CD4$^+$SLAMF7$^+$ $T_{EM}$ cells expressed cytolytic molecules. Clonally expanded CD8α$^-$ but not CD8α$^{low}$ CD4$^+$SLAMF7$^+$ $T_{EM}$ cells decreased following glucocorticoid-induced disease remission.

**Conclusions:** A subset of CD8α$^-$CD4$^+$SLAMF7$^+$ cytotoxic $T_{EM}$ cells is oligoclonally expanded in patients with active IgG4-RD. This population contracts following glucocorticoid-induced remission. Further characterisation of this cell population may provide prognostic information and targets for therapeutic intervention.

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