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The cellular protein (cFLIP) downregulates IFN-alpha, a signaling protein involved in the pathogenesis of SLE

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disorder that manifests itself within various organs of the body. It is observed in women more often than men. While clinical presentations may vary widely, hallmarks of SLE include joint pains, fever, and a pathognomonic malar "butterfly" rash. Additional organ involvement may include cardiac, renal, and neurological symptoms, where cardiac or renal involvement is oftentimes the cause of death.

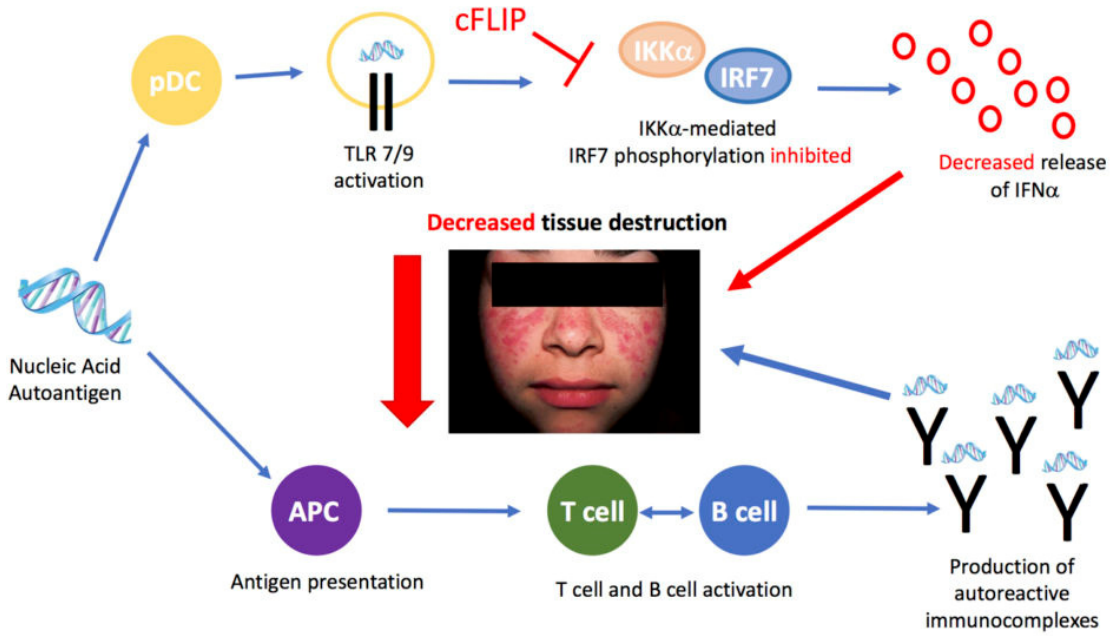

Fig1-cFLIP as therapeutic target in the treatment of SLE. An unknown autoantigen is taken up by antigen presenting cells (APC) which present the "foreign" material to T and B cells, leading to their activation. B cells and ultimately plasma cells produce large quantities of autoantibodies and immunocomplexes that contribute to host tissue damage. In addition, the same autoantigen activates TRL7 and TLR9 within plasmacytoid dendritic cells (pDCs). Activation of TLR7/9 leads to the activation of the kinase IKK-alpha which mediates IRF7 phosphorylation and ultimately production of IFN-alpha, an anti-viral cytokine that also contributes to the tissue damage seen in patients with SLE. By binding to the kinase, IKK-alpha, cFLIP prevents IRF7 phosphorylation, a critical event for the production of IFN-alpha. Our hypothesis is that by decreasing the level of IFN-alpha produced in patients with SLE, less tissue destruction may be observed.

To understand how to target SLE symptoms specifically, we must first describe the current dogma of pathogenesis. Briefly, an unknown autoantigen (viral, bacterial, or host nucleic acid) activates the dendritic/T cell/B cell antigen presentation axis that ultimately leads to the production of autoantibodies by activated B cells and plasma cells. Meanwhile, the same autoantigen is taken up by plasmacytoid dendritic cells (pDCs)

which leads to activation of the TLR7/9 pathway. This stimulates the transcription factor, IRF7, to drive expression of interferon a (IFNα) a major anti-viral protein that is markedly elevated within the tissues of patients with SLE. The combination of IFNα production with deposition of harmful immunocomplexes within affected organs leads to the tissue damage observed in individuals with SLE.

The current treatment for SLE patients is aimed at broadly targeting T and B cell immunity which has major immunosuppressive consequences. Considering these patients are already moderately immunosuppressed pre-treatment, a more specific target of therapy is ideal.

I and others in the field hypothesize that targeting IFNα production is a more specific way to decrease SLE-mediated tissue destruction while also avoiding the downfalls of general immunosuppressive drugs. I set out to understand how I might modulate the cell signaling pathway involved in the production of IFNα.

It is widely accepted that the cellular FLICE-like inhibitor protein, cFLIP, negatively regulates IFNβ production by binding to and inhibiting the IRF3 transcription factor. The IRF3 and IRF7 proteins are structurally very similar, but involved in different signaling pathways within the cell to express IFNβ vs. IFNα, respectively. Interestingly, I found that over-expression of cFLIP indeed inhibits IFNα expression. I went on to discover that cFLIP inhibits IRF7 activation much differently than it inhibits IRF3 activation. The TLR7/9 pathway of nucleic acid recognition is the predominate pathway within pDCs that leads to IFNα production. A critical kinase, IKKα, is stimulated in response to this event which is necessary for IRF7 phosphorylation and activation (and ultimately expression of IFNα). I found that cFLIP interacts with IKKα to prevent IRF7 activation, correlating with suppression of IFNα production within a pDC cell line.

In the future, it would be of great interest to test the effects of cFLIP over-expression in pDCs in an animal model of SLE, asking if tissue damage would be decreased in animals over-expressing cFLIP compared to untreated animals. One hope is that the side-effects of cFLIP-controlled IFNα expression would be minimal compared to other immunosuppressive drugs currently in use. Of course, there are several potential complicating factors. For example, IFNα is important for anti-viral defenses. Thus, using cFLIP as a therapeutic may put people at risk for more severe virus infections. Another concern is that cFLIP has other functions. cFLIP is an anti-apoptotic protein, and several cancers have increased cFLIP levels presumably to promote tumor cell survival. Thus, there should be careful monitoring of the transformation of cFLIP over-expressing cells into cancerous cells. Nevertheless, the potential for using cFLIP as a targeted treatment for SLE holds great promise.

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Publication

Cellular FLIP long isoform (cFLIPL)-IKKα interactions inhibit IRF7 activation, representing a new cellular strategy to inhibit IFNα expression.
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