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NET-released LL37 is a new SLE autoantigen for T-helper cells involved in autoantibody production

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Background: Inflamed lupus skin/kidney over-express LL37, an antimicrobial peptide (AMP) with immuno-modulatory functions. By binding to nucleic acids, LL37 triggers plasmacytoid dendritic cells (pDCs) activation and Type I interferon (IFN-I), a master factor in lupus, via TLR7/9. *In silico*/experimental data indicate that LL37 sequence harbors T-cell promiscuous epitopes behaving as T-cell autoantigens in psoriasis, an autoimmune disease characterized by high skin LL37 levels. In Systemic lupus erythematosus (SLE), LL37 is released during NETosis and becomes target of anti-LL37 antibodies that correlate with serum IFN-I and lupus disease activity (SLEDAI).

Objectives: We addressed LL37 capacity to act as T-cells autoantigen in SLE patients.

Methods: We assessed circulating SLE T-cell proliferation and cytokine production to LL37 and control AMPs by BrdU-incorporation-assay and ELISA/intracellular staining, respectively. We characterized SLE LL37-specific T-cell lines/clones and detected LL37-specific T-cells in blood by peptide-HLA-ClassII-tetramers; we addressed antibody reactivity to LL37 and DNA in SLE patients' sera and in *in vitro*-PBMC-cultures stimulated with LL37 or control AMPs by ELISA. We addressed presence of LL37 in lupus tissues by confocal microscopy.

Results: T-helper-17(Th17)/T-follicular-helper(Tfh)-like LL37-specific T-cells were present in 45% of SLE patients, correlated with SLEDAI and declined during stable remissions. LL37-specific T-cells correlated with (and help production of) NET-inducing anti-LL37 and anti-DNA antibodies.

Conclusions: LL37 is target of T-cells and autoantibodies with pathogenic functions in SLE. The data suggest that T-cell and anti-LL37-antibody reactivity can represent novel SLE disease markers and highlights the role of NETosis in inducing autoreactive T-cells in SLE and, possibly, in other autoimmune diseases.

Biography

Loredana Frasca obtained her Biological Science degree in 1992 and her PhD in Cellular Immunology in 1996. She has expertise in cellular immunology with particular focus on T-cells, antigen presentation and T-cell tolerance. She has also expertise in innate immunity, in particular in regulation of dendritic cells functions. In the last ten years she worked on activation and homeostasis of T-cells and dendritic cells in normal responses and autoimmunity. Most recent research is focused towards the identification of pathogenic pathways that activate both innate and adaptive immunity in autoimmune diseases such as psoriasis, lupus, systemic sclerosis and arthritis.

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