



# AB013. CXCL4-DNA immune complexes drive inflammation in systemic sclerosis by amplifying TLR9-mediated interferon- $\alpha$ production

Ernest Y. Lee<sup>1,2,3</sup>, Roberto Lande<sup>4</sup>, Carlo Chizzolini<sup>5</sup>, Gerard C. L. Wong<sup>1</sup>, Loredana Frasca<sup>4</sup>

<sup>1</sup>Department of Bioengineering, <sup>2</sup>Division of Dermatology, UCLA, Los Angeles, CA, USA; <sup>3</sup>UCLA-Caltech Medical Scientist Training Program, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA; <sup>4</sup>National Center for Drug Research and Evaluation, Istituto Superiore di Sanità, Rome, Italy; <sup>5</sup>Immunology & Allergy and Immunology & Pathology, University Hospital and School of Medicine, Geneva, Switzerland

*Correspondence to:* Roberto Lande; Loredana Frasca. National Center for Drug Research and Evaluation, Istituto Superiore di Sanità (ISS), viale Regina Elena 299, 00161 Rome, Italy. Email: roberto.lande@iss.it; loredana.frasca@iss.it; Gerard C. L. Wong. UCLA Bioengineering, 420 Westwood Plaza, 5121 Engineering V, UCLA, Los Angeles, CA 90095-1600, USA. Email: gclwong@seas.ucla.edu.

**Abstract:** Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by inflammation-driven tissue fibrosis and vasculopathy. CXCL4 is a chemokine overexpressed in SSc and represents an early serum biomarker of severe disease. CXCL4 likely contributes to inflammation via chemokine signaling pathways, but the exact role of CXCL4 in SSc pathogenesis is unclear. Here, we combine X-ray scattering, confocal microscopy, immune cell experiments, and analysis of SSc skin biopsies to elucidate an unanticipated mechanism for CXCL4-mediated immune amplification in SSc. We find that CXCL4 organizes “self” and microbial DNA into liquid crystalline immune

complexes that drastically amplify Toll-like receptor 9 (TLR9)-mediated plasmacytoid dendritic cell (pDC) hyperactivation and interferon- $\alpha$  production. Surprisingly, this immunomodulatory activity is independent of CXCR3, the CXCL4 receptor. Importantly, we find that CXCL4-DNA complexes are present *in vivo* and correlate with type I interferon (IFN-I) levels in SSc blood, and that CXCL4-positive skin pDCs coexpress IFN-I-related genes. Taken together, we establish a direct link between CXCL4 overexpression and the IFN-I-gene signature in SSc and identify a potential therapeutic opportunity to disrupt inflammation in SSc by inhibiting the self-assembly of CXCL4-DNA complexes. Our findings are consistent with an emerging general paradigm in which nucleic acid-scaffolding proteins like antimicrobial peptides, bacterial amyloids, and chemokines can drive autoimmunity by modulating innate immune receptors without being direct agonists.

**Keywords:** Systemic sclerosis (SSc); scleroderma; CXCL4; Toll-like receptor 9 (TLR9); self-assembly; immune complexes; nanocrystals

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