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Systemic Lupus Erythematosus and Type I Interferon

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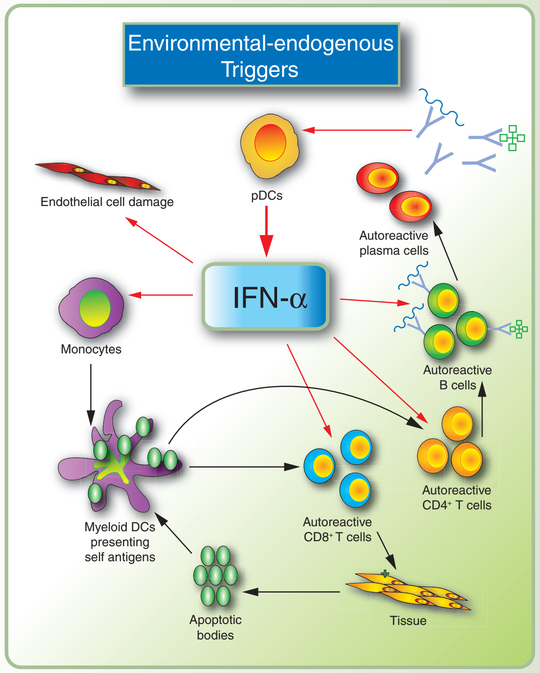
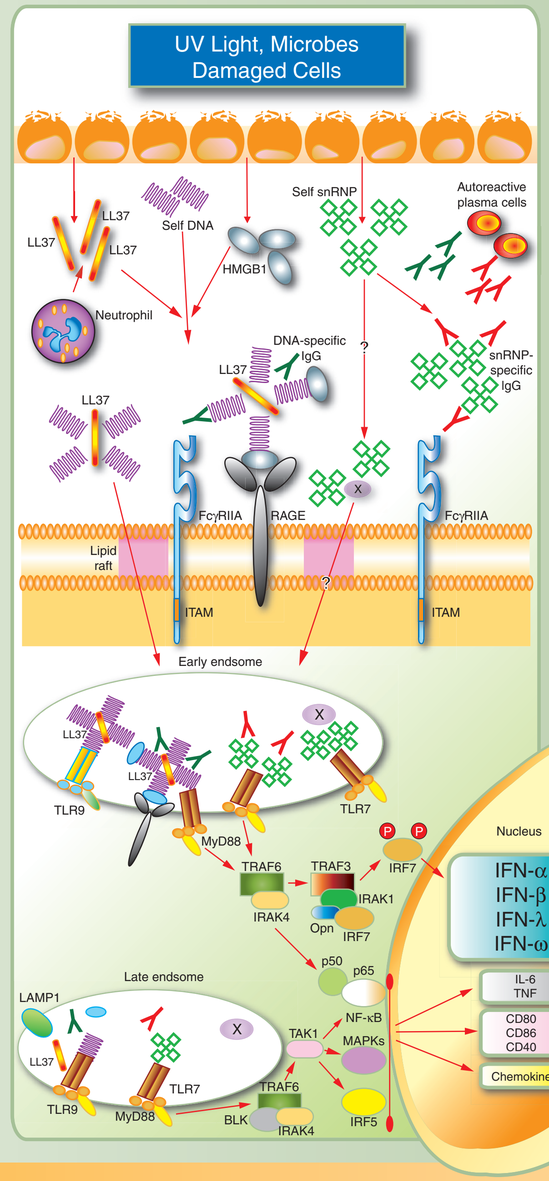
In recent years, the study of Systemic Lupus Erythematosus (SLE) patients has revealed a central role for Interferon alpha (IFN-α) in disease pathogenesis. Furthermore, endogenous nucleic acids and immune complexes (IC) activate Toll-Like Receptors (TLRs) and provide an amplification loop for Type I IFN production by plasmacytoid dendritic cells (pDCs) and for B cell activation in SLE. Indeed, a series of host factors have been recently described that modify self nucleic acids to gain entrance into endosomal compartments within pDCs, where they activate interferogenic TLR signalling. The unabated production of IFN-α induces the transcription of molecules that further contribute to amplify this pathogenic loop. Polymorphisms in genes controlling Type I IFN production or its downstream signaling pathway, such as IRF5, have been recently reported as conferring genetic susceptibility to SLE.



A. The central role of Type I IFN in SLE.

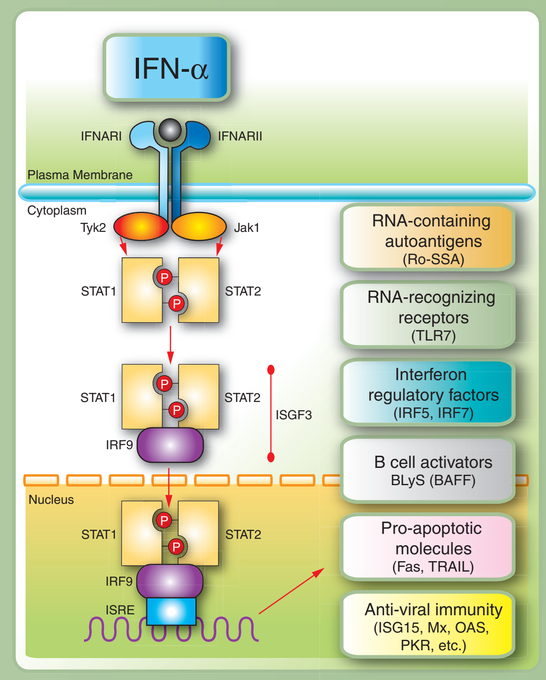
Under the steady state, immature myeloid dendritic cells (DCs) capture apoptotic bodies and present their autoantigens, without costimulatory molecules, to autoreactive T lymphocytes. This results in either their deletion or in the expansion of regulatory T cells. Upon exposure to environmental (i.e. viruses) and/or endogenous (i.e. nucleic acid-containing immune complexes) triggers, pDCs from Systemic Lupus Erythematosus (SLE) patients produce IFN-α in a sustained fashion. IFN-α activates myeloid DCs, which express co-stimulatory molecules and trigger the expansion and differentiation of autoreactive $CD4^+$ and $CD8^+$ T cells, and possibly mature B cells, into autoreactive effectors. Cytotoxic T cells kill tissue targets thereby generating nucleosomes and granzyme B-dependent autoantigen fragments, which further feed the autoimmune process. B cell tolerance check points are defective in SLE patients, leading to the expansion of anti-nuclear antibody expressing B cells. IFN-α, together with other products of activated pDCs such as IL-6, drive these autoreactive B cells to differentiate into plasma cells that secrete autoantibodies. DNA and RNA-containing immune complexes can further activate pDCs to release IFN-α, amplifying this pathogenic loop. IFN-α also directly promotes abnormal vasculogenesis, which might contribute to the development of premature atherosclerosis in SLE.



B. In SLE, both environmental (i.e. virus-derived) as well as endogenous (i.e dsDNA, snRPs) nucleic acids can trigger Type I IFN secretion from pDCs.

Nucleic acids of endogenous origin are released upon cell death (i.e. keratinocyte exposure to UV light). Several host factors have been implicated in converting self DNA into triggers of pDC activation, including DNA and/or RNA-containing immune complexes, the antimicrobial peptide LL37 and high mobility group box 1 protein (HMGB1). A direct link between LL37 and pDC activation in psoriasis was recently described. LL37 binds self-DNA fragments forming large aggregated structures that are resistant to extracellular nuclease degradation. Self-DNA–LL37 complexes can enter pDCs through lipid-raft endocytosis. Aggregated self-DNA–LL37 complexes are retained in the early endosomes of pDCs, and as described for A-type CpG ODNs, trigger the TLR9–MyD88–IRF7 pathway of Type I IFN production without inducing pDC maturation. Dying cells also release HMGB1, which binds aggregated self-DNA–LL37 complexes and promotes their association with Toll-Like Receptor 9 (TLR9) in early endosomes by binding to RAGE (receptor for advanced glycation end-products). In SLE, DNA-specific IgG autoantibodies produced by autoreactive B cells bind self-DNA–LL37–HMGB1 complexes and increase their translocation to TLR9-containing early endosomes through binding to FcγRIIA (low-affinity receptor for IgG). Similar mechanisms are likely to operate to induce Type I IFN production by pDCs in response to RNA-containing complexes, which in turn will bind TLR7 in early endosomes. Whether snRNPs associate with other endogenous proteins and can be internalized into early endosomes via lipid rafts is not known.

Prolonged TLR9/TLR7 signaling in the early endosome activates MyD88 (myeloid differentiation primary-response gene 88) and IRF7 (interferon-regulatory factor 7), which translocates to the nucleus and promotes efficient Type I interferon (IFN) transcription. Conversely, nucleic acids adopting less complex (linear) conformations quickly traffic through the early endosomes into the more acidic late endosomes or lysosomes. This presumably activates a different set of signal mediators, particularly NF-κB (nuclear factor-κB) and probably MAPKs (mitogen-activated protein kinases) and IRF5, leading to a distinct outcome of pDC activation and maturation and limited secretion of Type I IFN. The differential contribution of these two pDC cellular compartments to SLE remains to be fully elucidated. Late endosomal TLR7 and TLR9 activation by nucleic acids internalized via specific surface Ig receptors is likely to also represent an important mechanism of autoreactive B cell activation in SLE.



C. IFN-α signals through a heterodimer of IFN receptor 1 (IFNAR1) and IFNAR2.

Following binding by Type I IFNs, signal transduction is initiated by pre-associated tyrosine kinases (JAK1 and TYK2 (tyrosine kinase 2)), which phosphorylate IFNAR1 leading to the recruitment and phosphorylation of the signal transducers and activators of transcription (STAT1 and STAT2). STAT heterodimers associate with IFN-regulatory factor 9 (IRF9) to form IFN-stimulated gene factor 3 (ISGF3). These complexes translocate to the nucleus to induce IFN-stimulated genes from IFN-stimulated response elements (ISREs). However divergence from this simplified signaling pathway can occur as Type I IFNs may elicit STAT homodimerization, and can also activate other STAT proteins. In addition to classic anti-viral proteins (i.e. ISG15, IFN-stimulated protein of 15 kDa; Mx, myxovirus resistance; OAS, 2',5'-oligoadenylate synthetase; PKR, protein kinase R), Type I IFN induces the transcription of genes that might potentially play a role in SLE pathogenesis. These include, among others, i) endogenous ligands (autoantigens such as Ro/SSA) and receptors (TLR7) that trigger Type I IFN production, ii) signaling molecules within the Type I IFN pathway (i.e. IRF7 and IRF5), iii) B cell activators (BlyS/BAFF) and iv) pro-apoptotic molecules (Fas, TRAIL) that would increase the antigenic (nucleosome) load and therefore contribute to the generation of Type I IFN-inducing TLR-ligands.

Abbreviations:
BAFF, B cell activating factor; **BLK**, B cell lymphocyte kinase; **BLyS**, B lymphocyte stimulator; **FcγRIIA**, low affinity Fc receptor for IgG; **HMGB1**, high mobility group box 1; **IFN**, interferon; **IFNAR**, IFN-receptor; **IgG**, immunoglobulin G; **IRAK**, IL-1R-associated kinase; **IRF**, interferon-regulatory factor; **ISGF3**, IFN-stimulated regulatory factor 3; **IL-6**, interleukin 6; **ISRE**, IFN-stimulated response element; **ITAM**, Immunoreceptor tyrosine-based activation motif; **LAMP1**, lysosomal-associated membrane protein 1; **MAPKs**, mitogen-activated protein kinases; **Mx**, myxovirus resistance; **MyD88**, myeloid differentiation primary response gene; **NF-κB**, nuclear factor-kappaB; **OAS**, 2',5'-oligoadenylate synthetase; Opn, osteopontin; **pDC**, plasmacytoid dendritic cell; **PKR**, protein kinase R; **RAGE**; receptor for advanced glycation end-products; **STAT**, signal transducers and activators of transcription; **TAK1**, transforming growth factor-β–activated kinase 1; **TLR**, Toll-like receptor; **TNF**, tumor necrosis factor; **TRAF**, TNF receptor–associated factor.

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