Systemic Lupus Erythematosus and Type I Interferon

Virginia Pascal & Jacques Banchereau

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-nuclear acids to gain entrance into endosomal compartments within pDCs, where they act to interfere with TLR signaling. The unabated production of IFN-α induces the transcription of molecules that further contribute to amplify this pathogenic loop. Prolonged Type I IFN production or its downstream signaling pathway, such as IRF5, have been recently reported as conferring genetic susceptibility to SLE.

In SLE, both environmental (i.e. virus-derived) as well as endogenous (i.e. ssDNA, snRNPs) 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) and host factors have been implicated in converting self DNA into triggers of pDC activation, including DNA and/or RNA-containing immune complexes, the antineutrophil cytoplasmic antibody (ANCA) and high mobility group box 1 protein (HMGB1). A direct link between LL37 and pDC activation in postnatal 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 TLR7-/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 FcεRI (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 endosomes activates MyD88 (myeloid differentiation primary-response gene 88) and IRF7 (interferon regulatory factor 7), which translocate to the nucleus and promote efficient Type I Interferon (IFN) transcription. Conversely, nuclear 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 with regard to TLR7. It is likely that both IFN-α and IFN-β, 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 vacuolization, which might contribute to the development of pre-mature atherosclerosis in SLE.

Environmental-endogenous Triggers

UV Light, Microbes Damaged Cells

Plasmacytoid Dendritic Cells (pDCs)

Cytosol

Endosomes

Nucleus

DNA and RNA-containing immune complexes

Type I IFN production

IFN-α

IFN-β

IFN-λ

IFN-ε

Interferon regulatory factors (IRF5, IRF7)

B cell activators (BlyS/BAFF)

Anti-viral immunity (ISGs, IFN-α, IFN-β, etc.)

In the central role of Type I IFN in SLE.

Under the steady state, immature myeloid dendritic cells (DCs) capture apoptotic bodies and present their autotaxinogns, 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 T cells and CD4+ T cells, and possibly mature B cells, into autoreactive effectors. Cytotoxic T cells kill target cells thereby generating necroosomes and granulocyte B-dependent autotaxinogen fragments, which further lead to the autoimmune process. Bel cell tolerance checks 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 vacuolization, which might contribute to the development of pre-mature atherosclerosis in SLE.

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

Following binding by Type I IFNs, signal transduction is initiated by pro-serine kinase tyrosine kinases (JAK1 and TYK2 (tyrosine kinase 2)), which phosphorylate the IFN receptor (IFNAR), the key receptor for Type I IFNs, within the cytoplasm. Tyrosine phosphorylation of the IFN receptor leads to the recruitment and phosphorylation of the signal transducer and activator of transcription (STAT1 and STAT2). STAT heterodimers then associate with IFN regulatory factor 9 (IRF9) to form IFN-stimulated gene factor 3 (ISGF3). IRF9 also represents an adapter that helps to recruit the kinase to induce IFN-generated signaling molecules. These two complexes lead to the transcription of molecules that further contribute to amplify the Type I IFN signaling pathway. This includes, 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. IRF5 and IFN-α), iii) B cell activators (BlyS/BAFF) and iv) pro-apoptotic molecules (Fox, TRAIL). By increasing the expression of anti-angiogenic molecules and growing factors, this activation might contribute to the development of pre-mature atherosclerosis in SLE.

PBL, InterferonSource, a division of Pestka Biomedical Laboratories, Inc. based in Piscataway, New Jersey, USA, is the world’s largest producer of interferons and related products for the life sciences research market. Founded in 1990 by Dr. Sidney Pestka, PBL continues to deliver high quality and timely products to keep researchers moving forward. To that end, each year we aim to increase the quality and quantity of our products, to supplement our store of product information, and to provide scientists around the world with the support they require.