Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem involvement due to immune dysregulation. Neuropsychiatric systemic lupus erythematosus (NPSLE) includes neurological syndromes involving the central, peripheral and autonomic nervous system, as well as psychiatric syndromes observed in patients with SLE in which other causes have been excluded. The pathogenesis of NPSLE has been attributed to many different mechanisms. In particular, autoantibody-mediated vasculopathy seems to play a major role in the pathogenesis of the clinical features. Several autoantibody specificities have been reported in the serum and cerebrospinal fluid of NPSLE patients. Recently, we demonstrated an association between serum anti-endothelial antibodies (AECA) and psychosis or depression in SLE patients, strengthening the notion of a possible role of this class of autoantibodies in the pathogenesis of the disease. The study of these autoantibodies could be a useful diagnostic and prognostic tool in patients with NPSLE.
The most common findings are small spot T2-hyperintense lesions (gliotic foci) in the white subcortical matter, mainly concentrated in frontal-parietal regions. Other signs can be cortical atrophy, periventricular lesions, dilation of ventricular chambers, and ischemic lesions [4]. While gadolinium is extremely useful for the characterization of acute inflammatory lesions, only 19% of NPSLE patients are recognized by MRI. On the other hand, single photon emission-computed tomography (PET-CT) and in vivo magnetic resonance spectroscopy have demonstrated a sensitivity of almost 100% in active NPSLE, but low specificity, compared to MRI.

Neuropsychological tests have been standardized to examine five major areas: general intelligence, verbal learning/memory, visual-spatial skills, psychomotor speed/manual dexterity, and attention/mental flexibility. Furthermore, most of the immunochemical tests studied in NPSLE are considered investigational, except testing for antiphospholipid antibodies (aPL) and anti-ribosomal P antibodies (anti-P), which seem to play an important role in the pathogenesis of NPSLE.

**PATHOGENESIS**

Over the years, several groups have expanded our knowledge on the nature of NPSLE pathogenesis. Multiple mechanisms were proposed, including antibodies, vasculitis, thrombosis, hemorrhage, hypertension, accelerated atherosclerosis, choroid plexus dysfunction, neuroendocrine immune effects, direct central nervous system (CNS) tissue injury, and cytokine-mediated damage [2]. Rhiannon [5] distinguished primary from secondary mechanisms. The primary mechanisms include vascular occlusion/hemorrhage, autoantibody-mediated (primarily anti-neuronal antibodies), choroid plexus dysfunction, cytokine effects, neuroendocrine-immune imbalances, and direct neural tissue injury (mediated by oxidative stress, excitatory amino acid toxicity and matrix metalloproteinase injury). On the other hand, secondary mechanisms include infections, medications, thrombotic thrombocytopenic purpura, hypertension, uremia, fever, electrolyte imbalances, thyroid disease, berry aneurysm, fibromyalgia, cerebral lymphoma, subdural hematoma, atherosclerotic cerebrovascular accident/stroke (CVA), reactive depression, sleep apnea, and another primary psychiatric or neurologic disease. A variety of autoantibodies has been implicated in the pathogenesis of the disease [Table 2]. These were found in the serum and cerebrospinal fluid (CSF). Anti-neuronal antibodies are directed against brain synapses, neurofilaments, GFAP, MAP-2, and NMO. Non-neural-specific antibodies include anti-P, antiphospholipid antibodies (aPL), anti-dsDNA, anti-N-methyl-D-aspartate (NMDA, also known as anti-NR2), anti-gangliosides (GM-10) lymphocytotoxic antibodies, and anti-endothelial cell antibodies (AECA).

**A proper and quick diagnosis is essential for managing neuropsychiatric manifestations in SLE patients**

**THE ROLE OF AUTOANTIBODIES**

The reported prevalence of autoantibodies in NPSLE is highly variable, depending on different ethnic background, sensitivity and specificity of the assays, and the time of the analysis with respect to the manifestation of the clinical event. In 1979, Bresnihan et al. [6] first suggested the potential pathogenic relevance of anti-neuronal, anti-P and anti-glia fibrillary acid proteins, and aPL in the psychiatric manifestation of SLE. More recently AECAs have been studied and correlated with the occurrence of such clinical events. The etiopathogenic role of autoantibodies in NPSLE remains unclear. Anti-neuronal antibodies can be found in the brain of NZB/W mice, supporting a direct pathogenic role. Given their higher reactivity in the CSF of patients with NPSLE, an intrathecal synthesis has been proposed. Nevertheless, the finding of cross-reactivity of lymphocytotoxic antibodies, anti-neuronal antibodies and mycobacterial glycolipids, together with impairment of the blood-brain barrier (BBB) frequently observed in NPSLE, may suggest the hypothesis of an extrathecal synthesis of the autoantibodies.

**AUTOANTIBODIES TO BRAIN COMPONENTS**

- **ANTI-RIBOSOMAL P PROTEIN P0 ANTIBODIES (ANTI-P)**

  Anti-P are directed against three phosphoproteins located on the larger 60 S subunit of eukaryotic ribosomes (P0, P1, P2). The prevalence of anti-P in SLE patients ranges from 6% to 36% [7] and their specificity for SLE was recently estimated at 99.4% [8]. Only a few studies have noted their presence in other diseases.
e.g., autoimmune hepatitis and autism. The association between anti-P and lupus psychosis was first described by Bonfa and co-workers [9]. Yoshio et al. [10] suggested the existence of a strong association between immunoglobulin (Ig) G and IgM anti-P with CNS disease, excluding lupus psychosis, in SLE patients. Moreover, several studies have demonstrated a decrease in verbal memory, psychomotor speed, and olfaction in SLE patients compared with healthy subjects, correlating with disease activity and CNS involvement. Interestingly, a relationship between smell impairment and anti-P has been observed. These data were confirmed by a recent study in which affinity-purified human anti-P were injected intracerebroventricularly (ICV) in mice [11]. The results showed that these antibodies induce both depression-like behavior and impaired olfactory function. The ribosomal P0 protein has been identified by molecular cloning strategy as an endothelial autoantigen in SLE patients [12]. Moreover, purified IgG anti-P derived from patients with SLE seems to activate human umbilical vein endothelial cells (HUVEC), as well as monocytes, leading to intrathecal B lymphocyte activation upon increased interleukin-6 (IL-6) production. In our cohort, 7.8% of SLE patients were anti-P positive but no association with psychiatric disturbances was found [13]. Remarkably, all patients with lupus psychosis tested seronegative for these autoantibodies. Finally, a significant difference was documented between the enzyme-linked immunosorbent assay (ELISA) kits used for the detection of anti-P; hence, the need for standardization of laboratory assays in the future which will enable better assessment of both the presence of anti-P and their clinical significance [14].

**ANTI-GLIAL FIBRILLARY ACID PROTEIN ANTIBODIES (ANTI-GFAPS)**
The GFAPs are 50 kDa intracytoplasmic filamentous proteins of the astrocytes, which stabilize the cytoskeleton and maintain astrocyte cell shape through the interaction with nuclear and plasma membranes. At present, these are the most specific markers to recognize cells of astrocytic origin in both normal and pathologic conditions. GFAPs are up-regulated in gliotic hypertrophy and perivascular inflammation of Alzheimer’s disease and multiple sclerosis. In addition, anti-GFPA antibodies were observed in patients with these conditions. Recently, it was demonstrated that anti-GFAPs are increased in the CSF of NPSLE patients. Although we found anti-GFAPs in 15% of sera from our SLE cohort, no significant correlations with neurologic or psychiatric morbidity were observed.

**ANTI-N-METHYL-D-ASPARTATE (NMDA) ANTIBODIES**
DeGiorgio et al. [15] demonstrated in vitro that a subset of anti-DNA antibodies cross-reacts with N-methyl-D-aspartate (NMDA) and induces neuronal cell injury. These autoantibodies can be found occasionally in the CSF of SLE patients. Furthermore, it was shown that sera showing reactivity to DNA and NMDA receptor obtained from lupus patients can elicit cognitive impairment when intravenously injected in mice [16].

**ANTIPHOSPHOLIPID ANTIBODIES (APL)**
Antiphospholipid antibodies are a heterogeneous group of antibodies directed against anionic phospholipids, phospholipid-binding plasma proteins, and phospholipid-protein complexes [17]. The association between aPL and NPSLE was first reported in 1984, and it is clear today that their main pathogenic effect results in thrombosis. aPL may contribute to neurologic damage by reacting with brain cells via β2-glycoprotein I (β2GPI) interaction. We have demonstrated the expression of β2GPI mRNA by astrocytes and neuronal and endothelial cells, suggesting that these cells can be a target of autoantibodies in antiphospholipid syndrome (APS) [18,19]. No significant association was found between aPL and AECA [13], although it has been postulated that AECA reactivity might be partly caused by the binding to a complex of β2GPI with phospholipids on endothelial cells. Nonetheless, Meroni et al. [20] found AECA positivity in 5 of 14 SLE patients with CNS involvement. The authors demonstrated that aPL and AECA are associated with neurological manifestations in SLE patients.

In another study, human endothelial cells were incubated with mouse AECA monoclonal antibodies, and the translocation of phosphatidylserine (PS) was established through the binding of annexin V, which binds specifically to PS. A rabbit β2GPI antibody and biotin-conjugated F(ab')2 aPL derived from three patients were also used to detect β2GPI on the cells. The authors found that 20–36% of the cells expressed anionic PL following incubation with AECAs, suggesting that some of these may be pathogenic and may even have the potential to induce production of aPL [21]. These in vivo observations were further validated by studies conducted on mouse models of APS, showing the development of neurological dysfunction and hyperactive behavior associated with aPL, anti-β2GPI and AECA after passive immunization with human anticardiolipin (anti-CL) monoclonal antibodies. Interestingly, we recently investigated whether cognitive impairment in SLE is associated with serum autoantibodies, disease activity and chronic damage. Antinuclear antibodies (ANA), anti-dsDNA, anti-CL, anti-β2GPI, anti-P, AECA and anti-Nedd5 antibodies were evaluated, and SLEDAI-2000 and SLICC were used to assess disease activity and chronic damage, respectively. We reported a significant association between aPL, disease activity, and chronic damage with cognitive dysfunction in SLE. In particular, anti-CL IgM were found associated with visual-spatial domain impairment ($r = 0.331$, $P = 0.005$) [22], strengthening the view of aPL involvement in NPLE manifestations.
• **ANTI-NEDD5 ANTIBODIES**

Nedd5 is a septin that plays an essential role in cytokinesis in mammalian cells. During apoptosis, Nedd5 moves from the cytoplasm to the cell surface, a process that might explain its increased immunogenicity [23]. Although anti-Nedd5 autoantibodies are not specific to SLE, they are significantly associated with NPSLE and could serve as an immunological marker of psychiatric manifestations.

• **ANTI-NR2 GLUTAMATE RECEPTOR**

As mentioned earlier, in 2001 DeGiorgio et al. [15] showed that anti-dsDNA autoantibodies from sera of SLE patients cross-react with NR2 glutamate receptors and mediate apoptotic death of neurons in vivo as well as in vitro. Following these results, it was demonstrated that IgG anti-NR2 antibodies in the CNS of SLE patients induce EC activation. Moreover, by activating the nuclear factor κB (NF-κB) signaling pathway, these antibodies may lead to inflammation of the blood-brain barrier, thereby possibly initiating the pathogenesis of NPSLE [24]. Most studies found anti-NR2 antibodies in blood in approximately one-third of SLE patients, at a higher ratio than in patients with other autoimmune diseases. Anti-NR2 antibodies are observed more often in the CSF of NPSLE patients than in the CSF of patients without autoimmune, neurologic or psychiatric diseases. Moreover, SLE patients with acute CNS manifestations or septic meningitis may present higher intrathecal concentrations of anti-NR2 antibodies than SLE patients hospitalized for other reasons. Nonetheless, their role in cognitive dysfunction and psychiatric manifestation of SLE is still under debate.

### AECA AND NPSLE

AECA were first described in 1971 by Lindqvist and Osterland [25] in chronic tuberculosis. These antibodies target a heterogeneous group of antigens directed against different structural endothelial proteins, ranging from 10 [25] to 200 KDa, as well as adhering to endothelial cells detected in a variety of diseases sharing vessel wall damage. AECA have been detected in healthy individuals, as well as in autoimmune and systemic inflammatory diseases including nervous system diseases. The prevalence of AECA in SLE patients ranges from 17% to 75%. We recently reported an association between serum AECA with psychosis and depression in patients with SLE [13], strengthening the view of a possible role of AECA in the development of psychiatric disorders.

AECA were shown to be highly associated with NPSLE and their pathogenic role has been demonstrated

• **ANTIGEN CHARACTERIZATION**

AECA are generally not specific for endothelial cells and a variety of antigens can be found on different substrates. AECA antigenic specificity is also observed in fibroblasts, leukocytes and monocytes. AECA recognize antigens expressed constitutively, other cryptic antigens that are cytokine-induced, as well as adhesion molecules. Even the human leucocyte antigen class I and II (HLA) determinants as well as extracellular matrix components (i.e., collagen types II, IV and VII, vimentin or laminin) constitute endothelial cell antigens. Autoantibodies against these antigens have been reported in systemic sclerosis (SSc) and SLE. Several molecules could bind to endothelial cells and become the so-called planted target antigens for AECA via presumed charge-mediated mechanisms, a DNA-histone bridge, or a specific receptor. Some examples are myeloperoxidase, DNA and β2GPI, which might adhere to endothelial cells incubated with patient’s sera. AECA can recognize antigens present solely in microvascular but not macrovascular endothelial cells. It seems that phenotypic and functional differences – such as nutritional requirements and responses to growth and migration stimuli – between endothelial cell antigens from microvascular and macrovascular sites may be responsible for this phenomenon. Thus, the evaluation of endothelial cells from vessels of different sizes seems advised in AECA assays.

The development of techniques to identify new antigens targeted by AECA has allowed the building of expression libraries of complementary DNA to messenger RNA extracted from endothelial cells and then transfected into prokaryotic or eukaryotic cells. Belizna et al. [26] characterized the putative target antigens for AECA, recognizing a role for EC-specific plasminogen activator inhibitor, ribosomal P protein P0, ribosomal protein L6, elongation factor 1a, adenylcyclase-associated protein, DNA replication licensing factor, profilin II, and human EC-associated lupus autoantigens 1 and 255. Furthermore, it was shown that the levels of these antibodies directly correlate with AECA levels and clinical findings in patients affected with SLE and systemic vasculitis. Another technique, two-dimensional electrophoresis, seems to be promising. Indeed, combined with western blot analysis using protein extracts from a hybridoma cell line, it enables the identification of antigens such as calreticulin, tubulin, vimentin and Hsp70. Recently, RLIP76 was identified as a new AECA autoantigen. RLIP76 catalyzes the ATP-dependent transport of glutathione (GSH) conjugates including GS-4-hydroxy-κ-2,3-nonenal (GS-HNE) [27]. ELISA detected IgG specific to RLIP76 in 30% of patients with Behçet disease (BD), 17% with SSC, 21% with rheumatoid arthritis (RA), and 30% with SLE, but in none of the sera from patients with mononucleosis or from healthy subjects. These results suggest that RLIP76 may play a major role in endothelial dysfunction in distinct autoimmune diseases.

Another newly discovered endothelial antigen is RABPT5, an essential and rate-limiting component of early endosomal fusion that regulates the release of neurotransmitter and neuritis outgrowth. RABPT5 is massively redistributed in
the cytoplasm of endothelial cells during apoptosis, possibly explaining its immunogenicity. Anti-RABPT5 antibodies bind and hinder the function of the RABPT5 protein in the neurons. This chain of events leads to the inhibition of endosomal membrane fusion which performs a protective function against amyloid deposit. In addition, anti-RABPT5 might cross-react with neurocrescin, hampering its ability to generate damaged neurons, suggesting a pathogenic role for these antibodies. There is evidence for a specific clone of AECA directed to actin, particularly in patients with atherosclerosis. It is well known that the humoral immune response to endothelium has a pivotal role in the development of atherosclerosis. In a previous study by our group [22], we performed immunoscreening of a human umbilical artery endothelial cells (HUAEC) expression library with IgG from two patients with carotid atherosclerosis and identified a clone specific to actin. The actin-specific IgG reactivity was evaluated in patients with carotid atherosclerosis, and the results were compared with those obtained from SLE and T1DM patients and from healthy subjects. Actin-specific IgG reactivity was detected in a significantly higher percentage of sera from patients with atherosclerosis and SLE than from healthy subjects (26% and 39%, respectively, vs. 5% of healthy subjects; \( P = 0.012 \) and \( P < 0.0001 \)). Therefore, actin can represent an autoantigenic molecule of potential clinical interest in carotid atherosclerosis and SLE vasculitis.

Another endothelial antigen targeted by AECA is Sip-1. This is a nuclear splicing factor containing an arginine-serine-rich domain and a RNA-binding motif probably involved in transcription and pre-mRNA splicing. In a previous study, we demonstrated that IgG, IgM, and IgA specific to factor Sip1 C-ter were detectable in patients with several autoimmune diseases characterized by the presence of serum AECA, such as BD, SLE, SSc, and primary vasculitis as well as in patients with diseases that share some clinical features with BD (inflammatory bowel disease and uveitis). We also found that IgM immunoreactivity was significantly higher in patients with BD and in patients with primary vasculitis than in the other tested groups [28].

Finally, the presence of AECA has even been demonstrated in a small percentage of healthy individuals. The so-called natural AECA (NA) include polyreactive IgM, IgG, and/or IgA, which recognize a restricted and conserved set of endothelial antigens and express low affinity for their target antigens in most of the cases. NA may bind to circulating molecules such as hormones and cytokines, as well as lymphocytes and endothelial cells. Normal IgG interacts with living endothelial cells and is internalized with a mechanism involving microtubules and resembling that of ligand-receptor internalization. IgG-endothelial cell interaction appears to be dependent on the variable region of antibodies and is followed by modifications of endothelial cell function. Natural AECA increase anti-inflammatory properties of endothelial cells through the selective inhibition of thromboxane A2, endothelin and metalloproteinase-9 secretion, as well as through the inhibition of endothelial cell pro-inflammatory response to tumor necrosis factor-alpha (TNFa) [29]. Recently, Servettaz et al. [30] identified the targets of NA in cytoskeletal proteins (β-actin, vimentin, α-tubulin), prolyl-4 hydroxylase β-subunit (a member of the disulfide isomerase family) and two glycolytic enzymes (glyceraldehyde-3-phosphate-dehydrogenase and α-enolase). All these are ubiquitous proteins implicated in cell-cycle regulation, membrane fusion, microtubule bundling, nuclear RNA export and DNA replication and repair, regulation of coagulation (α-enolase is an activator of plasminogen), and cell growth. Thus, NA may participate in host defense against pathogens by opsonization, contributes to the clearance of senescent cells and immune complexes, and/or exerts anti-inflammatory and anti-thrombotic properties, together with preventing endothelial cell activation by TNFa. Finally, these antibodies may play a role in fetal tolerance and impaired immune regulation, such as diminished levels of serum IgM-AECA detected in SLE patients that may contribute to impaired reproductive function commonly seen in SLE [31].

**AECA: MULTIPLE MECHANISMS FOR A PLEIOTROPIC PLAYER**

AECA might contribute to the pathogenesis of systemic vasculitis and vasculitis-associated diseases through a) activation of ECs, b) direct cytotoxic effect due to complement-dependent cytotoxicity or indirect cytotoxic effect secondary to antibody-dependent cytotoxicity, c) induction of coagulation, and d) induction of apoptosis through the binding of phospholipids or heat-shock protein 60. Mechanisms of disease are summarized in Figure 1. Del Papa and colleagues [32] demonstrated that AECA can activate ECs by inducing the expression of adhesion molecules, such as E-selectin, intercellular adhesion molecule 1 and vascular cell adhesion molecule 1, in a dose-dependent fashion. Moreover, AECA can stimulate the production of cytokines, including interleukin (IL)-1b and IL-8, and chemokines such as monocyte-chemoattractant protein 1. Specifically, AECA might promote a pro-inflammatory and pro-adhesive EC phenotype through the induction of the mitogen-activated protein kinase cascade. Additionally, a number of cytokines, e.g., TNFa, can in turn activate NF-κB pathway and c-Jun N-terminal kinase-mitogen-activated protein kinases. The result is increased leukocyte adhesion to endothelial cells induced by the release of endothelium-derived mediators rather than complement-dependent cell-mediated EC damage. AECA have been associated with thrombosis, for instance by promoting the production of tissue factor (TF) and thereby favoring coagulation. It was also demonstrated that AECA is a genuine promoter of TF synthesis. Accordingly, high plasma levels of von Willebrand factor, thrombomodulin and tissue plasminogen activator (TPA) were detected in patients with SLE. Furthermore, TF activity, TF antigen and TF mRNA
were dose-dependent on AECA titers. Taken together, these data strongly suggest that activation of ECs leads to a procoagulant status. Furthermore, anti-heparin antibodies (AHA) can be found in patients with SLE and seem to correlate with renal and neurological disease. AHAs exert complement-dependent cytotoxicity on ECs and form immune complexes with heparin, one of the major glycosaminoglycans in ECs. It has been reported that the binding of AECA to EC can provoke cleavage and release of heparan sulphate and promote pro-inflammatory and procoagulant processes and apoptosis. This effect is specific for AECA since elution studies failed to show inhibition with anti-CL, anti-DNA, hyaluronate or chondroitine sulphate. AECAs also seem to correlate with anti-CL in SLE patients. Indeed, aPL can contribute to a pro-inflammatory and procoagulant endothelial phenotype by interfering with the binding of annexin V, synthesis of endothelin I, induction of apoptosis and the protein containment/surveillance system. AECAs may increase the expression of negative ionic phospholipids such as phosphatidylserine (PS) on the surface of ECs, leading to increased binding of anti-CL. It was reported that AECAs from the sera of patients with vasculitis can trigger the translocation of anionic phospholipids, most notably PS, from the inner to the outer leaflet of the plasma membrane, and consequently the binding of FITC-conjugated annexin V. Interestingly, the accessibility of PS to annexin V was restricted to those cells recognized by AECA. Moreover, autoantibodies targeting the heat-shock protein 60 (Hsp60) were recently identified in patients with SLE. These bind endothelial cells and induce PS exposure, followed by apoptosis, thus providing a target for anti-PS. Fas receptor can also be targeted by AECA; however, further activation does not seem to be a prerequisite for AECA-mediated apoptosis of ECs, and other authors have reported Fas-independent apoptosis. Finally, AECA could exert a direct cytotoxic effect through complement-dependent cytotoxicity, especially when ECs are stimulated with IL-1 or TNFα.

**DETECTION METHODS**

AECAs were identified using mouse frozen kidney sections as the substrate in the standard indirect immunofluorescence (IF) technique. The binding of AECA was demonstrated in the target cells through the F(ab)2 portion, rather than the Fc portion of the antibody. The most frequently used AECA detection methods are IF, ELISA, immunoblotting, radioimmunoassay, fluorescence-activated cell sorting, immunoprecipitation, complement-dependent cytotoxicity and the antibody-dependent cell-mediated cytotoxicity. Immunofluorescence was the first technique to be developed, but today AECAs are only rarely tested with this method. ELISA, performed on HUVEC as substrate, is the most commonly used. Other substrates can be employed, such as cell membrane extracts, cells from renal or medullary microvessels, and hybridoma cell lines. Generally, confluent EC monolayers are fixed before testing to avoid non-specific IgG-binding loss of cells. Nevertheless, fixation induces
permeabilization of EC membranes, which may allow AECA cross-reaction against intracellular compounds. To avoid these artifacts, ELISA with unfixed EC can be used. False-negative AECA results can be due to the lack of expression of certain target antigens on a specific substrate. For this reason, it has been recommended that several EC substrates be used simultaneously. False-positive AECA could occur owing to endogenous antibodies, such as anti-β2GPI, reacting with fetal calf serum (FCS) proteins from culture medium coated on ELISA plates. This error could be avoided by antibody absorption in FCS-containing dilution buffer or by washing cells of FCS before plating. Finally, there is a subpopulation of AECA that is likely to react with extracellular matrix components, such as collagen type II, IV, VII, and laminin, leading to false-positive results.

CONCLUSIONS
In the management of NPSLE, identification of the clinical features as well as achievement of early diagnosis is crucial for determining the optimal treatment. Several mechanisms are involved in the pathogenesis of these disorders. Most are autoantibody-dependent or related, and there is considerable evidence that AECA may play a key role in these processes. Nevertheless, low specificity, the lack of standardized detection methods, and the possible presence of NA secondary to SLE polyclonal B cell activation limit the use of AECA as diagnostic and prognostic markers. Clearly, further studies are necessary for fully understanding their role in SLE clinical practice.

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Glycemic control in diabetes is restored by therapeutic manipulation of cytokines that regulate beta cell stress

In type 2 diabetes, hyperglycemia is present when an increased demand for insulin, typically due to insulin resistance, is not met as a result of progressive pancreatic beta cell dysfunction. This defect in beta cell activity is typically characterized by impaired insulin biosynthesis and secretion, usually accompanied by oxidative and endoplasmic reticulum (ER) stress. Hasnain et al. demonstrated that multiple inflammatory cytokines elevated in diabetic pancreatic islets induce beta cell oxidative and ER stress, with interleukin-23 (IL-23), IL-24 and IL-33 being the most potent. Conversely, the authors show that islet-endogenous and exogenous IL-22, by regulating oxidative stress pathways, suppresses oxidative and ER stress caused by cytokines or glucolipotoxicity in mouse and human beta cells. In obese mice, antibody neutralization of IL-23 or IL-24 partially reduced beta cell ER stress and improved glucose tolerance, whereas IL-22 administration modulated oxidative stress regulatory genes in islets, suppressed ER stress and inflammation, promoted secretion of high quality efficacious insulin and fully restored glucose homeostasis followed by restitution of insulin sensitivity. Thus, therapeutic manipulation of immune regulators of beta cell stress reverses the hyperglycemia central to diabetes pathology.

Dietary modulation of the microbiome affects autoinflammatory disease

The incidences of chronic inflammatory disorders have increased considerably over the past three decades. Recent shifts in dietary consumption may have contributed importantly to this surge, but how dietary consumption modulates inflammatory disease is poorly defined. Pstpip2mo mice, which express a homozygous Leu98Pro missense mutation in the Pombe Cdc15 homology family protein PSTPIP2 (proline-serine-threonine phosphatase interacting protein 2), spontaneously develop osteomyelitis that resembles chronic recurrent multifocal osteomyelitis in humans. Recent reports demonstrated a crucial role for interleukin-1β (IL-1β) in osteomyelitis, but deletion of the inflammasome components caspase-1 and NLRP3 failed to rescue Pstpip2mo mice from inflammatory bone disease. Thus, the upstream mechanisms controlling IL-1β production in Pstpip2mo mice remain to be identified. In addition, the environmental factors driving IL-1β-dependent inflammatory bone erosion are unknown. Lukens et al. have shown that the intestinal microbiota of diseased Pstpip2mo mice was characterized by an outgrowth of Prevotella. Notably, Pstpip2mo mice that were fed a diet rich in fat and cholesterol maintained a normal body weight, but were markedly protected against inflammatory bone disease and bone erosion. Diet-induced protection against osteomyelitis was accompanied by marked reductions in intestinal Prevotella levels and significantly reduced pro-IL-1β expression in distant neutrophils. Furthermore, pro-IL-1β expression was also decreased in Pstpip2mo mice treated with antibiotics, and in wild-type mice that were kept under germ-free conditions. The authors further demonstrate that combined deletion of caspases 1 and 8 was required for protection against IL-1β-dependent inflammatory bone disease, whereas the deletion of either caspase alone or of elastase or neutrophil proteinase 3 failed to prevent inflammatory disease. Collectively, this work reveals diet-associated changes in the intestinal microbiome as a crucial factor regulating inflammasome- and caspase-8-mediated maturation of IL-1β and osteomyelitis in Pstpip2mo mice.