

REVIEW ARTICLE

Fcγ receptor biology and systemic lupus erythematosus

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Abstract

The maintenance of immune homeostasis and the regulation of pro-inflammatory responses that underlie autoimmune pathology require a coordinated interplay between cytokines, cellular receptors and downstream signaling pathways. The family of fragment crystallizable receptors for immunoglobulin G (IgG) (FcγR) represents a good example of how controlling the simultaneous triggering of activatory and/or inhibitory receptors results in a balanced immune response. FcγRs play a crucial role in linking the antibody-mediated recognition of pathogens, allergens or auto-antigens to the cellular arm of the immune response. In this review, we detail how dysfunction in FcγR pathways is linked to the development of the autoimmune disease, systemic lupus erythematosus.

Key words: autoimmune disease, biomarker, fragment crystallizable receptor (FcR), signaling, systemic lupus erythematosus (SLE).

FRAGMENT CRYSTALLIZABLE RECEPTORS IN HUMANS

Fragment crystallizable receptors (FcRs) are receptors on immune cells that bind to the Fc region of immunoglobulins. FcγRs bind to the most common type of immunoglobulin (IgG) and are expressed on the surface of many different immune cell types including monocytes, macrophages, dendritic cells (DC), natural killer cells and neutrophils.^{1–4} In broad terms, FcγRs can be separated into high or low affinity receptors based on their affinity for IgG or into activatory or inhibitory receptors based on their signaling activity and associated functions.⁵ In humans, three major classes of IgG-receptor have been described; FcγRI (CD64), FcγRII (CD 32), and FcγRIII (CD16). These classes can be further sub-divided into discrete isoforms such as FcγRIIA, FcγRIIB, FcγRIIC, FcγRIIIA and FcγRIIIB that exhibit significant differences in their affinity for individual IgG sub-classes and tissue distribution.

FcγRI, is a 72 kD type-I membrane glycoprotein that is a high affinity receptor capable of binding to monomeric IgG and is constitutively expressed on monocyte and macrophage lineage cells. FcγRI is a member of the multi-chain immune recognition receptor family, comprising hetero-oligomeric complexes of a ligand-binding chain, and a common γ-chain that is found in association with several other immune receptors. FcγRI triggers its principle intracellular signal transduction cascades through the common γ-chain that encodes an immune-receptor tyrosine-based activation motif (ITAM). FcγRIIIA is a low-affinity receptor expressed on natural killer (NK) cells and macrophages that also utilizes the common γ-chain to trigger signal transduction.^{6–8}

The most broadly distributed activatory receptor in humans is FcγRIIA which is expressed on monocytes, macrophages, neutrophils and platelets.⁹ This is a low-affinity receptor that preferentially binds to complexes of IgG, and along with FcγRIIC (found in NK cells) expresses an inherent ITAM in its cytoplasmic tail, thus FcγRIIA does not need to oligomerise with a γ-chain in order to signal.^{10,11}

FcγRIIIB is a GPI-linked receptor expressed principally on neutrophils and some eosinophils with no

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identified transmembrane domain.⁵ Since FcγRIIB does not contain a cytoplasmic tail, it is thought to signal through association with other surface proteins such as FcγRIIa and the type 3 complement receptor (CR3).^{12,13}

ACTIVATORY FCγR SIGNALLING AND FUNCTION

Fcγ receptor signaling is triggered upon aggregation or cross-linking of the surface receptors.¹⁴ Under physiological conditions, this occurs when multiple surface Fcγ receptors are engaged by multivalent antigens or IgG containing immune complexes (ICs). For low-affinity receptors such as FcγRII and FcγRIII, multiple IgG molecules linked to ICs can bind simultaneously to multiple Fcγ receptors. In contrast, the high-affinity receptor FcγRI, is normally occupied by monomeric IgG present at high concentrations in serum, and is thus activated when multiple FcγRI bound-IgG molecules bind the same multivalent antigen simultaneously.⁵

Upon receptor aggregation, downstream signaling is initiated by either the ITAM motifs on the activatory receptors, or the immune-tyrosine inhibitory motifs (ITIMs) on the inhibitory receptors. For the activatory receptors, regardless of whether the ITAM motifs are intrinsic to the receptors or whether they are present on the cytoplasmic tails of the associated γ-chain, the process of receptor aggregation causes the ITAMs to recruit Src-family kinases, which phosphorylate the ITAMs.⁶ The Src-family member that is recruited each time is unclear, as multiple Src-family kinases appear to be capable of phosphorylating the ITAMs. This may be dependent on the cell type involved, the exact Fcγ receptor that is activated, and the form of target antigen that is providing the stimulus.^{15–18} However, the current consensus is that *in vivo*, Lyn is the Src-family kinase most likely to be involved in the early phosphorylation of tyrosine residues on ITAM motifs.^{19,20}

Upon phosphorylation of ITAMs on activatory Fcγ receptors, Syk-family kinases are recruited, such as Syk itself.^{21,22} Syk in turn phosphorylates and activates downstream signaling mediators such as phosphoinositide-3-kinase (PI3K), which results in phospholipase-induced calcium signaling (PLD1 or PLCγ1) and the activation of calcium-dependent and calcium-independent isoforms of protein kinase C (PKC) dependent on the form of Fcγ receptor engaged. Syk also phosphorylates son of sevenless (SOS), the guanine nucleotide exchange factor (GEF) that activates mitogen activated protein (MAP) kinase signaling.^{5,23}

INHIBITORY FCγR SIGNALING AND FUNCTION

In humans and mice, the principal inhibitory Fc receptor is FcγRIIB. FcγRIIB is expressed on monocytes, macrophages, dendritic cells, neutrophils and B-lymphocytes. As part of a regulated immune response to complexes formed between pathogens and IgG we need simultaneous triggering of both activatory and inhibitory receptors. When FcγRIIB is co-ligated with the B cell receptor (BCR), it inhibits B cell proliferation and activation.²⁴ FcγRIIB may also regulate the activity of dendritic cells (DC)²⁵ where expression and aggregation controls immune complex-induced maturation.¹ FcγRIIB activity has been linked to an imbalance between tolerance and autoimmunity with dysfunction in this receptor associated with chronic inflammatory demyelinating polyneuropathy (CIDP)²⁶ and joint damage in rheumatoid arthritis.²⁷ The best correlation between impaired FcγRIIB function and autoimmune pathogenesis is seen in systemic lupus erythematosus (SLE).

FcγRIIB transmits its signal through an immunoreceptor tyrosine-based inhibitory motif (ITIM).^{28,29} Aggregation of the inhibitory receptor FcγRIIB with another ITAM-bearing receptor such as the BCR causes phosphorylation of its intrinsic ITIM motifs by Lyn.²⁹ This results in the recruitment of the inositol phosphatase SHIP to the ITIM motifs on FcγRIIB, where it proceeds to convert the signaling mediator phosphatidylinositol 3,4,5 triphosphate (PIP₃) into PI(3,4)P₂.³⁰ Since the recruitment of Bruton's tyrosine kinase (Btk) and PLCγ are dependent on PIP₃, the decrease in PIP₃ due to SRC-homology-2-domain containing inositol-5-phosphatase (SHIP) activity will prevent Btk and PLCγ activation, as well as inhibit calcium signaling. In this way, FcγRIIB acts to inhibit the activity of ITAM-bearing receptors such as the BCR and other activatory Fc receptors.

THE ROLE OF FCγ RECEPTORS IN IMMUNE DYSFUNCTION AND SLE

In human patients as well as in experimental animal models, FcγRs have been implicated in immune dysfunction and the development of autoimmunity. FcγRIIB expression on B cells has been shown to regulate the accumulation of autoreactive plasma cells³¹ and malfunctioning FcγRs result in impaired phagocytosis of apoptotic cells by monocyte-derived macrophages.³² FcγRIII mediates neutrophil recruitment

by immune complexes³³ and transgenic expression of FcγRIIB and FcγRIIA in Fcγ-chain-deficient mice restores susceptibility to progressive glomerulonephritis and the cutaneous reverse passive Arthus (RPA) reaction.³⁴ In mice, FcγR-bearing myeloid cells are responsible for triggering murine lupus nephritis³⁵ and in SLE patients, FcγRIIA is involved in the activation of interferon (IFN)-α production from plasmacytoid dendritic cells (pDC).³⁶ Mutations in FcγRs have been shown to alter the function of monocytic cells and B-lymphocytes. For example, FcγRIIA has two codominant alleles that differ by a single amino acid, termed R131 and H131³⁷ and allele R131 exhibits decreased binding affinities for human IgG2.^{3,37,38} Also the change of valine (V) to phenylalanine (F) at amino acid position 176 in FcγRIIA results in a receptor that binds IgG1, IgG3, and IgG4 with less avidity³⁹ than V/V homozygotes. Studies in human cohorts have shown that SLE is significantly associated with both alleles, R131 and F176, that encode lower affinity isoforms of FcγRIIA and FcγRIIA respectively.⁴⁰

Several additional genetic association studies link FcγR polymorphisms with susceptibility to SLE. SLE is a severe, chronic autoimmune disease that is characterized by overproduction of autoantibodies to nuclear constituents with associated tissue deposition and inflammation.^{41,42} In clinical practice, the American College of Rheumatology has proposed 11 Revised Diagnostic Criteria for the classification of SLE with four or more of the 11 criteria usually required over time for confirmation of the diagnosis.⁴³ In SLE, women have higher rates of disease than men (a ratio of 4 : 1 worldwide) and disease frequency and clinical manifestations vary greatly between racial groups with Asian populations exhibiting a higher frequency of severe disease versus European populations.⁴⁴ SLE etiology is still unknown and multiple gene candidates, located on several chromosomes, have been investigated.

In a meta-analysis carried out by Lehnbecher and colleagues, the development of SLE was significantly associated with the alleles encoding the low affinity isoforms of both FcγRIIA (FcγRIIA-R/R131) and FcγRIIA (FcγRIIA-F/F158).⁴⁰ More recently, a similar meta-analysis study carried out by Karassa and colleagues found that an FcγRIIA-R/H131 polymorphism represents a significant risk factor for the development of SLE but had no clear effect on susceptibility for lupus nephritis in a large patient cohort.⁴⁵ This study also intimated that there is no significant heterogeneity between racial subgroups and susceptibility to

SLE.⁴⁵ A genome-wide association scan of 317 501 single nucleotide polymorphisms (SNPs), included 720 women of European ancestry with SLE and 2337 controls carried out by Harley and colleagues found evidence for an association between an R131 FcγRIIA single nucleotide polymorphism and SLE with a *P*-value of $P < 1 \times 10^{-5}$.⁴⁶ When we combine the data from all of these studies, we can conclude that the FcγRIIA-R131 allele is a risk factor for SLE found in all human populations. Additional confirmation that FcγRIIB and FcγRIIB play an important role in SLE comes from a study on a Chinese patient cohort that showed that 50Ter-225Thr (34.1%, in FcγRIIB gene) and 72Arg-118Asn (40%, in the FcγRIIA gene) haplotype were more frequently transmitted in SLE than other haplotypes.⁴⁷

Polymorphisms in human and mouse FcγRIIB genes have been implicated in immune dysfunction and increased susceptibility to SLE. A single amino acid substitution at amino acid position 232 within the transmembrane domain of the FcγRIIB receptor⁴⁸ results in impaired receptor function.⁴⁹ FcγRIIB₂₃₂ is unable to inhibit other activatory receptors because it is excluded from sphingolipid rafts.⁴⁹ The defect in activatory receptor regulation and signaling enhances the inflammatory response and phagocytic activity of human macrophages. Experiments in transgenic mice, overexpressing FcγRIIB on B cells, show a reduced IgG component of T-dependent antibody responses plus early disease resolution in collagen induced arthritis (CIA). Moreover, these mice exhibited reduced spontaneous SLE. In the same mouse strains, FcγRIIB overexpression on macrophages (rather than B cells) had no effect on CIA and SLE but increased mortality after *S. pneumoniae* infection.⁵⁰ These results demonstrate contrasting roles for FcγRIIB in two different immune cell types, B cells and macrophages, with important implications for the development of SLE.

REGULATION OF EXPRESSION OF FcγRS AND SLE

Cytokine-mediated regulation of activatory and inhibitory Fcγ receptors is important in controlling the immune functions of monocytes and B cells. Results obtained in human monocyte cell lines show that tumor necrosis factor α (TNFα), interleukin 10 (IL-10) and IL-13 reduce the transcriptional activity of the FcγRIIB promoter, and thus would be beneficial under inflammatory conditions, but may also in the long-term increase susceptibility to autoimmunity.⁵¹ In

addition, TNF α in combination with IL-4 and IL-13, decreased the expression of activatory Fc γ Rs suggesting an anti-inflammatory effect.⁵¹ Negative regulation of B cell immune responses depends on the activity of four inhibitory receptors: CD22, Fc γ RIIB, CD72 and the paired immunoglobulin-like receptor (PIR)-B. Experiments in mice suggest that IL-4 enhances B cell immune responses by reducing expression of all four inhibitory receptors at the protein and mRNA level.⁵² Findings from previous studies suggest that the same cytokine within a different milieu can have opposing functions, while Fc γ RIIB activity is always associated with immune inhibition.

In Caucasian cohorts, a polymorphism in the regulatory region of the Fc γ RIIB promoter, known as the 2B.4 haplotype, is a risk factor for SLE and further implicates this receptor in disease pathogenesis.⁵³ When the relative expression levels of Fc γ RIIB are compared between patients and controls, healthy controls exhibit an up-regulation on memory B cell subsets as opposed to naïve B cells. In contrast active SLE patients show Fc γ RIIB down-regulation on both memory and plasma B-lymphocytes.⁵⁴ However, Fc γ RIIB expression on myeloid lineage cells in SLE and healthy controls is similar.⁵⁴ An important role for Fc γ RIIB is in controlling apoptosis of plasma cells. Survival of migratory plasma cells in bone marrow is independent of antigen⁵⁵ and highly dependent on factors⁵⁶ that form 'survival niches'. These survival niches in bone marrow have a limited capacity for plasma cells⁵⁶ and other redundant B cells are thus eliminated by apoptosis. Experiments in mice demonstrate that Fc γ RIIB controls persistence of bone marrow plasma cells with cross-linking of Fc γ RIIB inducing cell-autonomous apoptosis.⁵⁷ Persistence of bone marrow plasma cells and increased Ig production occurs in Fc γ RIIB^{-/-} mice after immunization⁵⁸ and these mice strains are prone to SLE.⁵⁹ We can extend these observations on plasma cells in mice to Fc γ RIIB dysfunction in humans that leads to accumulation of plasma cells and to the development of autoimmune disease.⁵⁷

CONCLUSIONS

Taken together, these data support the idea that both activatory (Fc γ RIIA and Fc γ RIIA) and inhibitory Fc γ Rs (Fc γ RIIB) can play important roles in the immune regulation and dysfunction associated with the development of SLE in human populations. In particular, Fc γ RIIB appears critical for maintaining the balance of an efficient inflammatory response and/or unwanted

autoimmunity. This is supported by multiple clinical studies that have shown that Fc γ RIIB is a reliable biomarker for SLE susceptibility in different ethnic groups. With regards to the pathological mechanisms that underlie SLE, Fc γ RIIB and its signaling pathway represent an important checkpoint in peripheral and central tolerance and in controlling the development of autoreactive antibodies.⁶⁰ This suggests that a better understanding of Fc γ RIIB function will aid the development of early-diagnostic methods and enable refinements in existing therapeutic protocols for SLE and other autoimmune diseases.

REFERENCES

- 1 Dhodapkar KM, Kaufman JL, Ehlers M, *et al.* (2005; Feb 22) Selective blockade of inhibitory Fc γ receptor enables human dendritic cell maturation with IL-12p70 production and immunity to antibody-coated tumor cells. *Proc Natl Acad Sci USA* **102** (8), 2910–15.
- 2 Boruchov AM, Heller G, Veri MC, Bonvini E, Ravetch JV, Young JW (2005; Oct) Activating and inhibitory IgG Fc receptors on human DCs mediate opposing functions. *J Clin Invest* **115** (10), 2914–23.
- 3 Parren PW, Warmerdam PA, Boeijs LC, *et al.* (1992; Oct) On the interaction of IgG subclasses with the low affinity Fc gamma RIa (CD32) on human monocytes, neutrophils, and platelets. Analysis of a functional polymorphism to human IgG2. *J Clin Invest* **90** (4), 1537–46.
- 4 van de Winkel JG, Capel PJ (1993; May) Human IgG Fc receptor heterogeneity: molecular aspects and clinical implications. *Immunol Today* **14** (5), 215–21.
- 5 Nimmerjahn F, Ravetch JV (2008; Jan) Fc γ receptors as regulators of immune responses. *Nat Rev Immunol* **8** (1), 34–47.
- 6 Strzelecka A, Kwiatkowska K, Sobota A (1997; Jan 2) Tyrosine phosphorylation and Fc γ receptor-mediated phagocytosis. *FEBS Lett* **400** (1), 11–14.
- 7 Cecchetti S, Spadaro F, Lugini L, Podo F, Ramoni C (2007; Oct) Functional role of phosphatidylcholine-specific phospholipase C in regulating CD16 membrane expression in natural killer cells. *Eur J Immunol* **37** (10), 2912–22.
- 8 Stewart-Akers AM, Cunningham A, Wasko MC, Morel PA (2004; Nov) Fc gamma R expression on NK cells influences disease severity in rheumatoid arthritis. *Genes Immun* **5** (7), 521–9.
- 9 Ravetch JV, Bolland S (2001) IgG Fc receptors. *Annu Rev Immunol* **19**, 275–90.
- 10 Gessner JE, Heiken H, Tamm A, Schmidt RE (1998; Jun) The IgG Fc receptor family. *Ann Hematol* **76** (6), 231–48.
- 11 Ravetch JV, Kinet JP (1991) Fc receptors. *Annu Rev Immunol* **9**, 457–92.

- 12 Stockinger H (1997) Interaction of GPI-anchored cell surface proteins and complement receptor type 3. *Exp Clin Immunogenet* 14 (1), 5–10.
- 13 Galon J, Gauchat JF, Mazieres N, *et al.* (1996; Aug 1) Soluble Fcγ receptor type III (FcγRIII, CD16) triggers cell activation through interaction with complement receptors. *J Immunol* 157 (3), 1184–92.
- 14 Sanchez-Mejorada G, Rosales C (1998; May) Signal transduction by immunoglobulin Fc receptors. *J Leukoc Biol* 63 (5), 521–33.
- 15 Majeed M, Cavegion E, Lowell CA, Berton G (2001; Nov) Role of Src kinases and Syk in Fcγ receptor-mediated phagocytosis and phagosome-lysosome fusion. *J Leukoc Biol* 70 (5), 801–11.
- 16 Garcia-Garcia E, Rosales C (2002; Dec) Signal transduction during Fc receptor-mediated phagocytosis. *J Leukoc Biol* 72 (6), 1092–108.
- 17 Hallal-Calleros C, Agramonte-Hevia J, Garay-Canales C, *et al.* (2005; Jul 15) Syk and Lyn phosphorylation induced by FcγRI and FcγRII crosslinking is determined by the differentiation state of U-937 monocytic cells. *Immunol Lett* 99 (2), 169–79.
- 18 Huang ZY, Hunter S, Kim MK, *et al.* (2004; Aug) The monocyte Fcγ receptors FcγRI/γ and FcγRIIA differ in their interaction with Syk and with Src-related tyrosine kinases. *J Leukoc Biol* 76 (2), 491–9.
- 19 Anthony RM, Nimmerjahn F, Ashline DJ, Reinhold VN, Paulson JC, Ravetch JV (2008; Apr 18) Recapitulation of IVIG anti-inflammatory activity with a recombinant IgG Fc. *Science* 320 (5874), 373–6.
- 20 Bewarder N, Weinrich V, Budde P, *et al.* (1996; Sep) In vivo and in vitro specificity of protein tyrosine kinases for immunoglobulin G receptor (FcγRII) phosphorylation. *Mol Cell Biol* 16 (9), 4735–43.
- 21 Crowley MT, Costello PS, Fitzer-Attas CJ, *et al.* (1997; Oct 6) A critical role for Syk in signal transduction and phagocytosis mediated by Fcγ receptors on macrophages. *J Exp Med* 186 (7), 1027–39.
- 22 Kiefer F, Brummell J, Al-Alawi N, *et al.* (1998; Jul) The Syk protein tyrosine kinase is essential for Fcγ receptor signaling in macrophages and neutrophils. *Mol Cell Biol* 18 (7), 4209–20.
- 23 Ivan E, Colovai AI (2006; Jul) Human Fc receptors: critical targets in the treatment of autoimmune diseases and transplant rejections. *Hum Immunol* 67 (7), 479–91.
- 24 Bolland S, Ravetch JV (1999) Inhibitory pathways triggered by ITIM-containing receptors. *Adv Immunol* 72, 149–77.
- 25 Kalergis AM, Ravetch JV (2002; Jun 17) Inducing tumor immunity through the selective engagement of activating Fcγ receptors on dendritic cells. *J Exp Med* 195 (12), 1653–9.
- 26 Tackenberg B, Jelcic I, Baerenwaldt A, *et al.* (2009; Mar 24) Impaired inhibitory Fcγ receptor IIB expression on B cells in chronic inflammatory demyelinating polyneuropathy. *Proc Natl Acad Sci USA* 106 (12), 4788–92.
- 27 Radstake TR, Franke B, Wenink MH, *et al.* (2006; Dec) The functional variant of the inhibitory Fcγ receptor IIb (CD32B) is associated with the rate of radiologic joint damage and dendritic cell function in rheumatoid arthritis. *Arthritis Rheum* 54 (12), 3828–37.
- 28 Daeron M, Latour S, Malbec O, *et al.* (1995; Nov) The same tyrosine-based inhibition motif, in the intracytoplasmic domain of Fc γRIIB, regulates negatively BCR-, TCR-, and FcR-dependent cell activation. *Immunity* 3 (5), 635–46.
- 29 Nimmerjahn F, Ravetch JV (2006; Jan) Fcγ receptors: old friends and new family members. *Immunity* 24 (1), 19–28.
- 30 Cady CT, Rice JS, Ott VL, Cambier JC (2008; Aug) Regulation of hematopoietic cell function by inhibitory immunoglobulin G receptors and their inositol lipid phosphatase effectors. *Immunol Rev* 224, 44–57.
- 31 Fukuyama H, Nimmerjahn F, Ravetch JV (2005; Jan) The inhibitory Fcγ receptor modulates autoimmunity by limiting the accumulation of immunoglobulin G+ anti-DNA plasma cells. *Nat Immunol* 6 (1), 99–106.
- 32 Herrmann M, Voll RE, Zoller OM, Hagenhofer M, Ponner BB, Kalden JR (1998; Jul) Impaired phagocytosis of apoptotic cell material by monocyte-derived macrophages from patients with systemic lupus erythematosus. *Arthritis Rheum* 41 (7), 1241–50.
- 33 Coxon A, Cullere X, Knight S, *et al.* (2001; Jun) Fc γRIII mediates neutrophil recruitment to immune complexes: a mechanism for neutrophil accumulation in immune-mediated inflammation. *Immunity* 14 (6), 693–704.
- 34 Tsuboi N, Asano K, Lauterbach M, Mayadas TN (2008; Jun) Human neutrophil Fcγ receptors initiate and play specialized nonredundant roles in antibody-mediated inflammatory diseases. *Immunity* 28 (6), 833–46.
- 35 Bergtold A, Gavhane A, D'Agati V, Madaio M, Clynes R (2006; Nov 15) FcR-bearing myeloid cells are responsible for triggering murine lupus nephritis. *J Immunol* 177 (10), 7287–95.
- 36 Bave U, Magnusson M, Eloranta ML, Perers A, Alm GV, Ronnblom L (2003; Sep 15) Fc γRIIa is expressed on natural IFN-α-producing cells (plasmacytoid dendritic cells) and is required for the IFN-α production induced by apoptotic cells combined with lupus IgG. *J Immunol* 171 (6), 3296–302.
- 37 Warmerdam PA, van de Winkel JG, Vlug A, Westerdaal NA, Capel PJ (1991; Aug 15) A single amino acid in the second Ig-like domain of the human Fc γ receptor II is critical for human IgG2 binding. *J Immunol* 147 (4), 1338–43.
- 38 Parren PW, Warmerdam PA, Boeijs LC, Capel PJ, van de Winkel JG, Aarden LA (1992; Feb 1) Characterization of

- IgG FcR-mediated proliferation of human T cells induced by mouse and human anti-CD3 monoclonal antibodies. Identification of a functional polymorphism to human IgG2 anti-CD3. *J Immunol* 148 (3), 695–701.
- 39 Wu J, Edberg JC, Redecha PB, *et al.* (1997; Sep 1) A novel polymorphism of FcgammaRIIIa (CD16) alters receptor function and predisposes to autoimmune disease. *J Clin Invest* 100 (5), 1059–70.
- 40 Lehnbecher T, Foster CB, Zhu S, *et al.* (1999; Dec 15) Variant genotypes of the low-affinity Fcgamma receptors in two control populations and a review of low-affinity Fcgamma receptor polymorphisms in control and disease populations. *Blood* 94 (12), 4220–32.
- 41 Tsokos GC (2001; Dec) Systemic lupus erythematosus. A disease with a complex pathogenesis. *Lancet* 358 (Suppl), S65.
- 42 Salmon JE, Pricop L (2001; Apr) Human receptors for immunoglobulin G: key elements in the pathogenesis of rheumatic disease. *Arthritis Rheum* 44 (4), 739–50.
- 43 Hochberg MC (1997; Sep) Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 40 (9), 1725.
- 44 Castro J, Balada E, Ordi-Ros J, Vilardell-Tarres M (2008; May) The complex immunogenetic basis of systemic lupus erythematosus. *Autoimmun Rev* 7 (5), 345–51.
- 45 Karassa FB, Trikalinos TA, Ioannidis JP (2002; Jun) Role of the Fcgamma receptor IIa polymorphism in susceptibility to systemic lupus erythematosus and lupus nephritis: a meta-analysis. *Arthritis Rheum* 46 (6), 1563–71.
- 46 Harley JB, Alarcon-Riquelme ME, Criswell LA, *et al.* (2008; Feb) Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PTK, KIAA1542 and other loci. *Nat Genet* 40 (2), 204–10.
- 47 Pan F, Tang X, Zhang K, *et al.* (2008; Aug) Genetic susceptibility and haplotype analysis between Fcgamma receptor IIB and IIIA gene with systemic lupus erythematosus in Chinese population. *Lupus* 17 (8), 733–8.
- 48 Kyogoku C, Dijstelbloem HM, Tsuchiya N, *et al.* (2002; May) Fcgamma receptor gene polymorphisms in Japanese patients with systemic lupus erythematosus: contribution of FCGR2B to genetic susceptibility. *Arthritis Rheum* 46 (5), 1242–54.
- 49 Floto RA, Clatworthy MR, Heilbronn KR, *et al.* (2005; Oct) Loss of function of a lupus-associated FcgammaRIIb polymorphism through exclusion from lipid rafts. *Nat Med* 11 (10), 1056–8.
- 50 Brownlie RJ, Lawlor KE, Niederer HA, *et al.* (2008; Apr 14) Distinct cell-specific control of autoimmunity and infection by FcgammaRIIb. *J Exp Med* 205 (4), 883–95.
- 51 Liu Y, Masuda E, Blank MC, *et al.* (2005; May) Cytokine-mediated regulation of activating and inhibitory Fc gamma receptors in human monocytes. *J Leukoc Biol* 77 (5), 767–76.
- 52 Rudge EU, Cutler AJ, Pritchard NR, Smith KG (2002; Apr 15) Interleukin 4 reduces expression of inhibitory receptors on B cells and abolishes CD22 and Fc gamma RII-mediated B cell suppression. *J Exp Med* 195 (8), 1079–85.
- 53 Su K, Wu J, Edberg JC, *et al.* (2004; Jun 1) A promoter haplotype of the immunoreceptor tyrosine-based inhibitory motif-bearing FcgammaRIIb alters receptor expression and associates with autoimmunity. I. Regulatory FCGR2B polymorphisms and their association with systemic lupus erythematosus. *J Immunol* 172 (11), 7186–91.
- 54 Su K, Yang H, Li X, *et al.* (2007; Mar 1) Expression profile of FcgammaRIIb on leukocytes and its dysregulation in systemic lupus erythematosus. *J Immunol* 178 (5), 3272–80.
- 55 Manz RA, Lohning M, Cassese G, Thiel A, Radbruch A (1998; Nov) Survival of long-lived plasma cells is independent of antigen. *Int Immunol* 10 (11), 1703–11.
- 56 Radbruch A, Muehlinghaus G, Luger EO, *et al.* (2006; Oct) Competence and competition: the challenge of becoming a long-lived plasma cell. *Nat Rev Immunol* 6 (10), 741–50.
- 57 Xiang Z, Cutler AJ, Brownlie RJ, *et al.* (2007; Apr) FcgammaRIIb controls bone marrow plasma cell persistence and apoptosis. *Nat Immunol* 8 (4), 419–29.
- 58 Takai T, Ono M, Hikida M, Ohmori H, Ravetch JV (1996; Jan 25) Augmented humoral and anaphylactic responses in Fc gamma RII-deficient mice. *Nature* 379 (6563), 346–9.
- 59 Hoyer BF, Moser K, Hauser AE, *et al.* (2004; Jun 7) Short-lived plasmablasts and long-lived plasma cells contribute to chronic humoral autoimmunity in NZB/W mice. *J Exp Med* 199 (11), 1577–84.
- 60 Goodnow CC, Sprent J, Fazekas de St Groth B, Vinuesa CG (2005; Jun 2) Cellular and genetic mechanisms of self tolerance and autoimmunity. *Nature* 435 (7042), 590–7.