Receptors for gamma-globulin in the central and peripheral nervous system

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A heterogeneous group of receptors binding the Fc region of immunoglobulin (Ig), Fc receptors provide important links between the cellular and the humoral branches of the immune system. The members of this receptor group, specific for essentially all the Ig isotypes, are expressed on a variety of cells and mediate multiple important functions.

Receptors for IgG (FcyR), a subgroup within the larger group of Fc receptors, belong to the Ig supergene family. The receptors have repeating extracellular domains, a membrane spanning portion and a cytoplasmic tail and the genes encoding the receptors have been assigned to chromosome 1.1

When FcyR interact with the ligand, causing crosslinking of the receptors, a variety of biological responses are triggered. These include phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), release of cytotoxic and inflammatory mediators, enhanced antigen presentation, immune regulation and transfer of IgG. For immune regulation, it has been shown that the FcyR can interfere with maturation of T and B lymphocytes as well as antibody production in an isotypic specific way.1

Three major classes of leucocyte FcyR are currently recognised on the basis of ligand affinity, reactivity with monoclonal antibodies (mAbs) and cloning of complementary DNA (cDNA).1 FcyRI (CD64) are 70 kDa molecules expressed on monocytes and macrophages with high affinity for IgG and can be induced on neutrophils by interferon-γ (IFN-γ). FcyRII (CD32) have a molecular weight of 40 kDa and are encoded by three genes. FcyRIIB are expressed on lymphocytes, FcyRIIA and FcyRIIC are expressed on neutrophils, while monocytes and macrophages express all three variations. FcyRIII (CD16), of molecular weight between 45–80 kDa, have two distinct forms. FcyRIIB found on neutrophils are anchored to the membrane by glycosyl-phosphatidylinositol whereas FcyRIIA expressed on natural killer (NK) cells and macrophages are transmembrane proteins. Both FcyRII and FcyRIII have low affinity for IgG. Current information indicates that the three classes of FcyR do not perform discrete tasks. Rather, their functions seem dictated by the cell type on which they are displayed.

FcyR are also present on non-lymphoid cells in different organs, for example on trophoblasts and endothelial cells in human placenta and on keratinocytes in human skin. In this review we report the presence and possible functions of FcyR in the human nervous system.

FcyR in the central nervous system

FcyR have been demonstrated on cells in the choroid plexus, arachnoid granulations, leptomeninges, on perivascular macrophages, microglia and on endothelial cells. FcyR have also been found on microglia in culture.7 The receptors were demonstrated by haemadsorption of IgG-coated indicator cells, by binding of soluble immune complexes of horseradish peroxidase (HRP) anti-HRP and serologically using mAbs. Microglia and perivascular macrophages were stained by mAbs to FcyRI, FcyRII and FcyRIII, whereas endothelial cells were stained by anti-FcyRIII mAbs only.5 Oligodendrocytes, astrocytes and neurons do not express FcyR. Recently, FcyRIII mRNA was demonstrated in microglia using in situ hybridisation.6 The same radiolabelled cDNA probe for FcyRIII hybridised with a 1.4 kb RNA band in Northern blots prepared from total RNA from brain, indicating that the receptors are produced in the CNS.6

FcyR in the peripheral nervous system

FcyR have also been demonstrated on Schwann cells, perineurial cells, endothelial cells and on scattered endoneurial macrophages.8,9 The receptors were found on the surface membrane, inner membrane (axolemma) and on vesicles within the cytoplasm of Schwann cells by electron microscopy.10,11 Schwann cells in culture apparently lose their FcyR expression.12 Whether this is due to dedifferentiation of the cells or to loss of Schwann cell—axon interaction is not known. FcyR have been recognised in fetal nerves at approximately 10 weeks of gestation13 showing that the receptors are an innate component of the PNS. Mabs against FcyRI, FcyRII and FcyRIII stained scattered endoneurial macrophages, whereas only mAbs against low affinity FcyR stained Schwann cells, perineurial cells and endothelial cells.9 A radiolabelled cDNA probe for FcyRIII hybridised with a 1.4 kb RNA band in Northern blots prepared from total RNA from peripheral nerve. The steady state level of the 1.4 kb FcyRIII mRNA was found to be developmentally regulated by densitometry.13 In situ hybridisation experiments have demonstrated increased numbers of endoneurial FcyRII mRNAs positive macrophages in Wallerian degeneration,13 and in experimental allergic neuritis (EAN).14

Functions of FcyR in the nervous system

To date little is known about the functions of FcyR in the CNS and PNS. The FcyR in the
through a damaged blood-brain or blood-nerve barrier. Binding of IgG Fc fragments to FcγR in the CNS and PNS could: 1) block the various effects that are mediated by crosslinked FcγR such as phagocytosis, enhanced antigen presentation, ADCC and release of cytotoxic and inflammatory mediators; and 2) release sFcyR that may neutralise autoantibodies or immune complexes and downregulate a local Ig production.