Invited Review

CD15-containing glycoconjugates in the central nervous system

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Summary. CD15-containing glycoconjugates have a common trisaccharide residue, 3-fucosyl-N-acetyllactosamine, which can be recognized by a panel of monoclonal antibodies. Immunohistochemical studies revealed a widespread distribution of CD15 in several epithelial non-neural tissues as well as in the CNS. In the mature mammalian brain CD15-containing glycolipids and glycoproteins are constantly present in astrocytes, whereas oligodendrocytes and particular subpopulations of neurons are variably immunostained. CD15 immunoreactive astrocytes are spatially distributed in some brain regions, which points to specialized functions of astroglial subpopulations. The expression of CD15 follows a timely ordered pattern during the development of glial cells and neurons of certain brain areas, such as the human and rat cerebellum and the mouse visual system. During morphogenesis, CD15 may exert either growth-promoting or growth-repulsive activities to guide cell migration. In CNS lesions altered expression patterns of CD15 may occur. For example, in human gliomas the staining intensity for CD15 inversely correlates with the grade of malignancy. In degenerative brain diseases reactive astrocytes may reveal an increased labelling intensity on their cell surface as well as an abnormal cytosolic accumulation of the epitope. The functional significance of CD15 in the CNS is not exactly known yet. The carbohydrate could be involved in cellular adhesion and/or as receptor molecule in signal transduction pathways, as has recently been demonstrated for leukocyte-platelet or leukocyte-endothelial cell interactions.

Key words: 3-fucosyl-N-acetyllactosamine, CD15, Cell adhesion molecule, Central nervous system, Immunohistochemistry

Introduction

Since the early seventies, it is known that cell communication processes are mediated by carbohydrate structures on the cell surface and in the extracellular matrix (for review, see Jessell et al., 1990). In the highly-organized structures of the central nervous system (CNS), glycoconjugates play an important role in cell recognition and cell sorting processes during development as well as in the maintenance of specific control functions in the adult state.

The carbohydrate molecule 3-fucosyl-N-acetyllactosamine (CD15) was initially detected on embryonal carcinoma cells of mouse and human origin and in preimplantation mouse embryos from the 8-cell to the 32-cell stage (Solter and Knowles, 1978). Therefore, the antigen detected by these antibodies was designated as stage-specific embryonic antigen-1 (SSEA-1).

Afterwards, several other monoclonal antibodies were generated, which all bound to 3-fucosyl-N-acetyllactosamine and hence were assigned to the «Cluster of Differentiation 15» (CD15) by the International Leukocyte Typing Workshops (Gooi et al., 1981; Feizi, 1985; Kerr and McCarthy, 1985; Skubitz et al., 1989; Kerr and Stocks, 1992; Ball, 1995). Subsequent immunohistochemical investigations in humans and rodents exhibited a widespread distribution of CD15 in various non-neural tissues, such as epithelial cells of the digestive and urinary tract, the reproductive system, some endocrine glands, skin appendages, and myeloid cells (Fox et al., 1983; Howie et al., 1984; Howie and Brown, 1985; Kerr and McCarthy, 1985; Itzkowitz et al., 1986; Sewell et al., 1987). Since the trisaccharide was found in malignant tumors as well as during certain stages of embryogenesis, CD15 was denoted as an onco-developmental antigen (Feizi, 1985; Fukuda, 1985; Hakomori, 1986). In the adult CNS of various species, CD15 was immunocytochemically detected in glial and certain neuronal cells (Niedieck and Löhler, 1987; Mai and Reifenberger, 1988; Gocht and
Löhler, 1993; Gocht et al., 1994). In the developing CNS of humans and rodents, CD15 is temporospatially expressed by glial and neuronal subpopulations (Lagenaur et al., 1982; Yamamoto et al., 1985; Gocht et al., 1992; Satoh and Kim, 1994).

Until now, rather little is known about the functional role of CD15. Some recent data on the putative functions of CD15 during leukocyte-endothelium interactions suggest that the trisaccharide is involved in cellular adhesion, mediation of signal transduction, and possibly is a recognition marker for intracellular transport mechanisms. This paper reviews the present knowledge of the biological characteristics of CD15 with special emphasis on morphological and functional aspects in the CNS.

CD15-containing glycoconjugates and synthetic pathway of CD15

Originally, CD15 was detected by the standard chemical and immunohistochemical methods as free (non-cell-bound) oligosaccharide on glycoproteins in the fluid of ovarian cysts (Lloyd and Kabat, 1968; Lloyd et al., 1968). After introduction of the hybridoma cell technique for generation of monoclonal antibodies by Köhler and Milstein (1975), Solter and Knowles (1978) were the first who produced a monoclonal antibody (anti-SSEA-1 antibody), which specifically reacted to the carbohydrate sequence 3-fucosyl-N-acetyllactosamine. In other laboratories monoclonal antibodies were generated, which recognized a positional isomer of the blood group Lewis a (LeA) antigen and which therefore was designated as X-hapten or Lewis x (LeX) antigen. However, later on it has been demonstrated that the Lewis x antigen is genetically unrelated to the AB0 and Lewis blood group systems and thus does not represent a subgroup of Lewis antigens (for review see Feizi, 1985; Makita and Taniguchi, 1985; Thurin, 1988).

Until now, several other monoclonal antibodies have been produced (e.g. AHN-1, My-1, VEP8, VEP9, VIM-C6, MMA, Anti-Leu M1, and others), which all bind specifically to 3-fucosyl-N-acetyllactosamine and accordingly, were classified as «Cluster of Differentiation (CD) 15» (Goosi et al., 1981; Feizi, 1985; Kerr and McCarthy, 1985; Skubitz et al., 1989; Kerr and Stocks, 1992; Ball, 1995). Most of these antibodies are of the IgM isotype; however, lately two antibodies have been added to the list which are of the IgG isotype (MCS-1 and 7C3) (reviewed by Ball, 1995). Monoclonal antibodies to CD15 have been used for extensive immunohistochemical in situ localization studies and also for immunochemical analyses of the carrier molecules, i.e. glycoproteins and glycolipids to which the oligosaccharide may be bound. Macromolecules carrying the CD15 determinant were identified either as glycolipids of granulocytes (Urdal et al., 1983; Skubitz and August, 1985; Symington et al., 1985; Skubitz et al., 1989), normal and malignant gastrointestinal epithelia (Hansson et al., 1983; Iizkowitz et al., 1986) virus-transformed fibroblasts (Andrews et al., 1989) or as glycoproteins of granulocytes (Urdal et al., 1983; Skubitz and August, 1985; Albrechtsen and Kerr, 1989; Skubitz et al., 1989), ovarian cysts (Lloyd and Kabat, 1968), and as free oligosaccharide in human milk, urine, and meconium (Kobata and Ginsburg, 1969; Hallgren and Lundblad, 1977; Gooi et al., 1981). In the CNS of embryonic and neonatal rats CD15 is expressed on glycolipids (Yamamoto et al., 1985), whereas in adult rats CD15 is bound to glycoproteins (Mai and Schönlaub, 1992) but not to glycolipids (Knipe and Gocht, unpublished data). These data suggest that CD15 expression either on glycolipids or on glycoproteins is temporally regulated during development.

The CD15 epitope is synthesized by the transfer of fucose on type 2 chain of the blood group H. This reaction is mediated by an α3-fucosyltransferase, of which currently three types, i.e. plasma-, Lewis-, and myeloid-type, are known (Mollicone et al., 1988, 1990; de Vries and van den Eijnden, 1992). In leukocytes and in the brain this reaction is catalyzed by the α3-fucosyltransferase of the myeloid type (Mollicone et al., 1988, 1990; de Vries and van den Eijnden, 1992) (α3-fucosyltransferase of the myeloid-type has not been classified yet by the Nomenclature Committee of the International Union of Biochemistry). The metabolic pathway is defined as follows:

\[
\begin{align*}
\text{Type 2 chain} & \rightarrow \alpha3-\text{FT} + \text{GDP-Fuc} \\
\text{CD15} & \rightarrow \alpha3-\text{FT} + \text{GDP-Fuc} \\
\end{align*}
\]

In humans, the gene of α3-fucosyltransferase, which is held to be of the myeloid-type, has been located on chromosome 11 (Geurts van Kessel et al., 1984; Tettero and Geurts van Kessel, 1992). The subcellular localization of α3-fucosyltransferase in brain cells is still not known. Recently, the in situ localizations of all three types of α3-fucosyltransferase have been described in the developing human kidney, which revealed a sequential appearance of the enzymes during renal organogenesis (Candelier et al., 1993).

The attachment of sialic acid to the galactose residue of CD15 leads to sialyl-CD15. However, none of the hetero isolated α3-sialyltransferases is able to directly act on CD15 to produce the sialylated form. Therefore, in the biosynthesis of the α3-sialylated structures sialylation has to precede fucosylation of the Ga1b1→4GlcNAc based type 2 chain. Alternatively, a yet unidentified α3-sialyltransferase or other α3-sialylating system is involved in the synthesis of sialyl-CD15 (reviewed by the Vries and van den Eijnden, 1992).

Both CD15 and sialyl-CD15 are co-localized in various normal and neoplastic tissues (Howie and Brown, 1985; Iizkowitz et al., 1986; Yuan et al., 1987), except the CNS, where both antigens seem to be
differentially expressed. In cultured fetal human brain cells, CD15 is detectable in astrocytes and oligodendrocytes, but antibodies to the sialylated form of oligomeric CD15 almost exclusively stain microglial cells (Satoh and Kim, 1994). The expression pattern of both CD15 and sialyl-CD15 during morphogenesis has been studied only in the human lung and kidney, in which the carbohydrate moieties are sequentially expressed with CD15 appearing first, then followed by its sialylated form (Miyake et al., 1988; Candelieri et al., 1993).

CD15 is expressed in various normal and neoplastic non-neural tissues

Since the first description of the molecule by Solter and Knowles in 1978, CD15 has been detected in a great variety of human and rodent tissues. In humans, the trisaccharide is present mainly in the gastrointestinal and urogenital tract, in certain exocrine glands, and in myeloid cells (Table 1) (Fox et al., 1983; Combs et al., 1984; Howie et al., 1984; Howie and Brown, 1985; Kerr and McCarthy, 1985; Itzkowitz et al., 1986; Sewell et al., 1987; Märtensson et al., 1995). Substantial work has been put into the characterization of the CD15 expression on cells of the hematopoietic system, where CD15 is mainly expressed on polymorphonuclear leukocytes, monocytes, and on very early cells of the hematopoietic lineage (CD34-positive cells). Other blood cells, such as erythrocytes, platelets and lymphocytes stain negatively with antibodies to the CD15 epitope (Ball, 1995).

Increased immunoreactivity of CD15 has been found in several epithelial tumors, such as polyps and carcinoma of the colon, carcinoma of the kidney, urinary bladder, mammary gland, uterus, and lung and in neoplastic lesions of the hematopoietic and lymphatic system, such as myelogenous leukemia and Hodgkin's disease (Fox et al., 1983; Håansson et al., 1983; Hsu and Jaffe, 1984; Shi et al., 1984; McCarthy et al., 1985; Wiezorek et al., 1985; Itzkowitz et al., 1986; Sewell et al., 1987; Miyake et al., 1988; Yuan et al., 1987; LeBrun et al., 1992; Loy et al., 1995). In all these neoplastic lesions CD15 represents a tumor-associated antigen since minor amounts of the molecule are detectable in the corresponding normal tissues. De novo synthesis of CD15 has been suggested for the papillary carcinoma of the thyroid (Schröder et al., 1987). In some instances CD15 or its sialylated form (sialyl-CD15) may be released by the tumor cells, since elevated plasma levels of CD15 and sialyl-CD15 have been found in cancers of the gastrointestinal and biliary tract, pancreas, ovary, and lung (Chia et al., 1985; Fukushima et al., 1985; Kannagi et al., 1986). In most carcinomas a positive correlation between malignant potential and the amount of polyfucosylated long-chain CD15 antigens has been described (Fukushima et al., 1984; Itzkowitz et al., 1986; Yuan et al., 1987). Increased production of CD15 and other glycoconjugates in neoplastic cells could be due to activation of certain oncogenes regulating the transcription of specific glycosyltransferases (Yogeeswaran, 1983; Smets and van Beek, 1984; Hakomori, 1985; Makita and Taniguchi, 1985).

### Table 1. Distribution of CD15 in normal human non-neural tissues.

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Normal Human Non-Neural Tissues</th>
<th>Neoplastic Lesions</th>
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<tbody>
<tr>
<td><strong>Digestive tract</strong></td>
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<tr>
<td>Esophagus</td>
<td>Squamous cells</td>
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<td>Stomach</td>
<td>Epithelial cells of crypts</td>
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<tr>
<td>Duodenum</td>
<td>Enterocytes, Brunner's glands</td>
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<td>Jejunum</td>
<td>Argentaffin and goblet cells</td>
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<tr>
<td>Colon</td>
<td>Enterocytes (particularity of crypts)</td>
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<tr>
<td>Gallbladder</td>
<td>Epithelial cells</td>
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<tr>
<td><strong>Salivary glands</strong></td>
<td>Epithelial cells of ducts</td>
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<td><strong>Pancreas</strong></td>
<td>Acinar cells</td>
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<td><strong>Reproductive system</strong></td>
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<tr>
<td>Endocervix</td>
<td>Squamous cells</td>
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<td>Endocervix</td>
<td>Endocervical cells</td>
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<tr>
<td>Corpus uteri</td>
<td>Endometrial glands</td>
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<td>Ovary</td>
<td>Peritoneal cells, follicles</td>
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<td>Fallopian tube</td>
<td>Epithelial cells</td>
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<tr>
<td>Epididymis</td>
<td>Epithelial cells</td>
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<td>Prostate</td>
<td>Glandular cells</td>
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<td><strong>Urinary tract</strong></td>
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<td>Kidney</td>
<td>Proximal tubular epithelium,</td>
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<td>epithelial cells of loop of Henle</td>
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<td>Pelvis</td>
<td>Urothelial cells</td>
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<td>Ureter</td>
<td>Urothelial cells</td>
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<tr>
<td>Bladder</td>
<td>Urothelial cells</td>
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<td><strong>Mammary gland</strong></td>
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<td>Lactating</td>
<td>Lobular cells</td>
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<td>Resting</td>
<td>Duct cells</td>
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<tr>
<td><strong>Respiratory tract</strong></td>
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<td>Bronchi</td>
<td>Bronchial epithelium, mucous</td>
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<td>glands</td>
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<td>Skin</td>
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<td>Skin appendages</td>
<td>Sweat glands</td>
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<tr>
<td><strong>Hematopoietic/lymphoid organs</strong></td>
<td>Neutrophils, macrophages/histiocytes</td>
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<td>Myeloid cells</td>
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<td><strong>Endocrine glands</strong></td>
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<td>Adrenal gland</td>
<td>Medullary cells</td>
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<td>Pituitary gland</td>
<td>Cells of anterior pituitary</td>
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For references see text.

CD15 is region-specifically distributed in the CNS

The distribution CD15 has been immunohistochemically studied in the mature brain of several species, such as human, monkey, rat, and mouse (Lagenaar et al., 1982; Kerr and McCarthy, 1985; Niedeck and Löhler, 1987; Mai and Reifenberger, 1988; Gocht, 1992a,b; Marani and Mai, 1992; Gocht et al., 1994). In the human brain, CD15 immunoreactivity is found in glial cells and some subsets of neurons, e.g. substantia nigra (Fig. 1a), olfactory bulb (mitral cells), and the raphe nuclei of the pons, which functionally belong to the dopaminergic, glutaminergic, and serotonergic system respectively (Nieuwenhuys, 1985). Additionally, CD15 is found in acetylcholine-containing neurons of the basal forebrain and within septo- hypothalamic neurons, which contain neurophysin (Mai and Reifenberger, 1988). In neurons, CD15 is associated with the cell surface and/or with coarse granules within
Fig. 1. CD15 immunoreactivity in neurons and glial cells in the adult human brain. a. Several neurons of the substantia nigra are depicted revealing a granular staining within their cytoplasm (arrows). Note the natural black colour of melanin granules (arrowheads). X 390. b. Anterior commissure containing numerous oligodendrocytes with intracytoplasmic labelling (arrows). X 270. c. Within the optic nerve fibrous astrocytes are detectable, which exhibit immunoreactivity on their perikarya and processes. X 270
Fig. 2. Distribution of CD15-positive protoplasmic astrocytes within different areas of the isocortex of an adult human. In general, immunostained astrocytes are predominantly located within the cortical laminae I and VI, which is true for all cortical areas. Additionally, CD15-positive astrocytes are concentrated in the internal pyramidal layer (V) of the primary motor cortex (a) and in Brodmann's area 5/7 (b), and in the internal granular layer (IV) of the primary sensory cortex (c). In the primary visual cortex (Brodmann's area 17) immunostained astrocytes are almost exclusively present in layers I and VI (d). a, x 20; b-c, x 40
the cytoplasm.

In oligodendrocytes immunostaining is homogenously distributed within the cytoplasm (Fig. 1b). Interestingly, immunolabelling is more pronounced in distinct white matter tracts, such as the lateral portion of the pons (i.e. pedunculus cerebellaris medius and fibrae pontis transversae), the anterior commissure, and the deep cerebellar white matter. Individual cells of the ependymal lining are strongly CD15-positive either on their cell surface or intracytoplasmically (Mai and Reifenberger, 1988; Gocht et al., 1992). CD15 is expressed on protoplasmic and fibrous astrocytes, which reveal a granular decoration of the cell surface of their perikarya and processes (Fig. 1c). CD15-positive astrocytes seem to be concentrated in certain brain areas which serve specific functions. For example, in the isocortex CD15 immunoreactive astrocytes are predominantly located within the cortical laminae I and VI (Fig. 2). The lamina I is composed largely of axons that run laterally through the layer, i.e. parallel to the pial surface and of glial cells, whereas neurons are only sparsely present (Braak, 1980; Kelly, 1991). The layer VI contains pyramidal cells from which descending projections to the thalamus originate (Martin and Jessell, 1991). In addition to this principal patterning, immunostained astrocytes preferably reside in the internal pyramidal layer (V) of the primary motor cortex (Brodmann’s area 4) (Fig. 2a) containing the Betz cells, from which axons emerge, which contribute to the corticospinal tract. In the primary somatic sensory cortex (area 2) CD15-positive astrocytes are concentrated in the internal granular layer (IV) (Fig. 2c), which receives most of the afferent thalamocortical fibers (Kelly, 1991).

In the adult rat CNS, CD15 immunostaining is restricted to astrocytes (Niedieck and Löhrer, 1987; Gocht, 1992a,b, Gocht et al., 1994; Gocht and Löhrer, 1993). In most white matter tracts fibrous astrocytes exhibit a granular staining of the surface of their perikarya and processes, which ultrastructurally is localized at various attachment sites, such as astrocytes to astrocytes, astrocytes to cell bodies of oligodendrocytes, astrocytes to myelin sheaths, and astrocytes to blood vessels (Gocht and Löhrer, 1993; Gocht et al., 1994). Within grey matter areas of the brain and spinal cord a more speckled staining pattern is observed, which derives from labelling of the strongly branching processes of protoplasmic astrocytes (Fig. 3). In certain cortical areas distinct regional differences in the distribution pattern of CD15 are evident. For example, in the frontal and parietal cortex immunostaining of the neuropil is nearly homogeneously distributed throughout all layers, while in the occipital cortex a patch-like labelling is predominantly present in layers II, III and V (Gocht et al., 1994). With other glial markers, such as GFAP and S-100 protein, no or a different zonal organization of the glial cells occurs. Immunostains for GFAP reveal scattered astrocytes in all cortical layers with a slightly stronger staining of the subpial astrocytes within the molecular layer (I) (Gocht et al., 1994). This patterning is about the same in each telencephalic subdivision. Antibodies to S-100 protein stain numerous astrocytes in all cortical layers of the telencephalic cortex. A similar incongruent patterning of CD15-, GFAP-, and S-100 protein-positive astrocytes is also found in the hippocampus (Fig. 4). CD15-positive glial cells are concentrated within the molecular layer of the dentate gyrus and in the layer of the pyramidal cells (Fig. 4a). In contrast, GFAP-positive astrocytes are preferably located in the stratum oriens, in the stratum lacunosum moleculare, and in the hilus and the granular layer of the dentate gyrus (Fig. 4b). S-100 protein immunoreactive astrocytes are almost evenly distributed throughout the hippocampus, without any preponderance (Fig. 4c). In the rat cerebellum, CD15 immunostaining is almost exclusively restricted to the stratum moleculare and to the Purkinje cell layer (see Fig. 7f), which corresponds to labelling of the perikarya and processes of Bergmann glial cells (Gocht et al., 1994). Only a few labelled fibrous astrocytes are encountered in the deep cerebellar white matter. Again a different labelling pattern is observed when antibodies to GFAP and S-100 protein are employed. Both marker proteins are detectable in Bergmann glial cells and additionally in protoplasmic astrocytes of the granular layer as well as in fibrous astrocytes of the white matter (Gocht, 1992a; Gocht et al., 1994). In the rat retina CD15 immunoreactivity is concentrated along a rather small band of the inner plexiform layer adjacent to the ganglion cell layer (Fig. 5a), which may represent labelling of amacrine cells. Interestingly, a similar staining pattern has been observed for certain calcium-binding proteins (Schreiner et al., 1985). A dissimilar patterning is observed with antibodies to GFAP and S-100 protein, which apparently label the process and/or the perikarya of Müller glial cells (Fig. 5b,c).

Taken together, these examples support the suggestion that each brain regions contains its own «unique» astrocyte population, which is suited for special functions (reviewed by Hansson, 1988; Wilkin et al., 1990).

**Cell type-associated expression of CD15 in vitro**

In several in vitro studies it was tested whether certain subpopulations of CD15 immunoreactive glial cells could be identified as in the in vivo situation. In dissociation cultures of the rat optic nerve, CD15 is expressed by both type-1- and type-2-astrocytes (Gocht et al., 1994). Interestingly, we found only about 20 to 30% CD15-positive cells in pure astrocytic cultures kept for 4 days in vitro and prepared from optic nerves or whole brains of 2-day-old rats. Increasingly more astrocytes are immunolabelled if the time of cultivation is extended. In optic nerve explants cultured over a period of 5 weeks, most GFAP-positive cells co-express CD15. Similarly, the number of CD15-positive astrocytes increases if older animals, i.e. 10 to 19 days postnatal, are used to prepare tissue cultures. If astrocytes are co-cultured with meninges, a vigorous branching of astrocytic processes can be observed (Abnet et al., 1991;
Struckhoff, 1993, 1995). Remarkably, these astrocytes do not react with antibodies to A2B5 and thus cannot be taken as type-2 astrocytes. These process-bearing GFAP+/A2B5-astrocytes exhibit strong CD15 staining at the growing tips of their processes (Fig. 6a,b). Remarkably, these tips do not contain detectable amounts of GFAP. A similarly strong CD15 immunoreactivity at the terminating processes of cultured astrocytes has been observed after addition of retinoic acid to the culture medium (Stark et al., 1992).

Cell type-associated expression of CD15 is also found in primarily cultured neural cells of fetal human brains (12th to 15th week of gestation) grown in serum-containing media for 3 to 4 weeks (Satoh and Kim, 1994). In this culture system CD15 is detectable in 17% of astrocytes and in 100% of oligodendrocytes, whereas most of the microglial cells express only the sialylated form of oligomeric CD15. In contrast, no immunolabelling of neurons is seen, neither with antibodies against CD15 nor sialylated oligomeric CD15.

The putative functions of CD15 in cultured glial cells have been previously described by Niedieck and

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**Fig. 3.** CD15 immunoreactivity in the isocortex of an adult rat. a. In the occipital cortex, layers II and III contain numerous intensely-stained protoplasmic astrocytes. x 400. b. Electron microscopical visualization of CD15 immunoreactivity in the frontal cerebral cortex. Reaction product is located in spaces around axons (Ax) and dendrites (D), presumably representing glial processes. x 45,800
Fig. 4. Hippocampus of an adult rat immunostained for CD15 (a), GFAP (b), and S-100 protein (c). a. CD15-positive protoplasmic astrocytes are concentrated in the layer of the pyramidal cells (small arrows) and within the molecular layer of the dentate gyrus (large arrows). X 60. b. GFAP-immunoreactive astrocytes are predominantly found in the stratum oriens (open arrows), in the stratum lacunosum moleculare (curved arrows), and in the hilus and granular layer of the dentate gyrus (arrows). X 60. c. Astrocytes stained for S-100 protein are evenly distributed without any predominance. X 60
Fig. 5. Retina of an adult rat immunostained for CD15 (a), GFAP (b), and S-100 protein (c).  

a. CD15 immunoreactivity is observed along a small strip in the inner plexiform layer (IPL) at the border of the ganglion cells. x 375.

b. Antibodies against GFAP label cell processes of the Müller glia in the stratum limitans internum. x 375.

c. Antibodies to S-100 protein stain perikarya and processes of Müller cells (arrows). x 375
Löhler (1987). In mixed glial cell cultures, which are obtained from whole rat brains and kept in serum-containing medium for 3 to 6 days, CD15 immunoreactivity is found on astrocytes as well as on oligodendrocytes. Immunolabelling on oligodendrocytes decreases with ongoing time of cultivation and from the 9th day onwards no immunostaining is detectable. In contrast, astrocytes exhibit a constantly strong staining intensity particularly at their contact sites to each other over an incubation time of 12 days. After 8 days in vitro oligodendrocytes grow on top of CD15-positive astrocytes, which at these contact sites reveal oligodendrocyte-shaped «negative print» images. Since these «negative print» images are even present when the oligodendrocytes are mechanically removed from the underlying astrocytes, it seems unlikely that the negative prints are caused by inhibition of antibody diffusion. These observations suggest that in vitro CD15 is involved in selective and time regulated glia-glia cell interactions. In early cultures of rat glial cells, oligodendrocyte-astrocyte interaction could be of homophilic, i.e. CD15-CD15, type. In long-term cultures, the CD15-CD15 interaction could be replaced by a heterophilic binding, such as a CD15-integrin interaction, which exerts stronger adhesive properties (Fenderson et al., 1990; Lawrence and Springer, 1991; Hakomori, 1992).

**CD15 is developmentally regulated in the mammalian brain**

The first evidence that CD15 was an onco-developmental antigen came from Solter and Knowles (1978) who detected the epitope on embryonal carcinoma cells of murine and human origin and on the cells of preimplantation mouse embryos during compaction. Subsequently, developmental expression patterns of CD15 have been reported for the CNS and extraneural tissues, such as the human lung and kidney (Miyake et al., 1988; Candelier et al., 1993).

The role of CD15 during development of the CNS has been most thoroughly investigated in mouse, rat and man. From these studies strong evidence has been derived that the carbohydrate is involved in selective

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**Fig. 6. Double-immunofluorescence labelling of GFAP and CD15 in cultured astrocytes.** Optic nerve explants were taken from 19-day-old rats and grown for 5 weeks on a layer of rat meningeal cells in a serum-containing medium. **a.** Visualization of GFAP with FITC-conjugated antibodies shows an astrocyte at the center with its clearly stained intermediate filament cytoskeleton. **b.** Immunolabelling of CD15 with Cy-3-conjugated antibodies. Reaction product is detectable on the surface of the same cell. Note that multiple delicate CD15-positive processes terminate with small knobs, which are not stained with antibodies against GFAP. a, b, x 530
Fig. 7. CD15 immunoreactivity in rat retina during postnatal development. a. In an one-day-old rat immunostaining is present in the neuroepithelium (N), inner plexiform layer (IPL), ganglion cell layer (G), and nerve fiber layer (NF). The pigment epithelium (P) is not labelled. x 150. b. Retina of a 5-day-old rat, in which labelling is restricted to the inner plexiform layer (IPL) and to the nerve fiber layer (arrows). G: ganglion cell layer. x 240. c. In a 21-day-old rat immunostaining is only present in a small zone of the inner plexiform layer (IPL) adjacent to the ganglion cell layer (G). A similar staining pattern is present in the adult rat (see Fig. 5a). x 375
Fig. 8. Patterning of CD15 during postnatal development of the rat cerebellar vermis cut at parasagittal planes. 

**a,b.** One-day-old rat. The low power view (a) shows immunolabelling of the prospective medullary layer (M) as well as in all cortical layers. In a higher magnification (b) immunostained processes of the Bergmann glial cells (arrows) are visible traversing the outer granular layer.

**c.** In a 5-day-old rat strong staining is found within the medullary layer (M) at the onset of myelination.

**d.** 12-day-old rat showing intense labelling of the molecular layer (ML). Immunostained Bergmann glial processes traverse the outer granular layer (arrows). The inner granular layer (IGL) presents a reticular labelling pattern. The medullary layer (M) is only faintly decorated.

**e.** In a 14-day-old rat maximal staining intensity is attained within the inner granular layer. In the molecular layer (ML) the mature complement of immunoreactivity is acquired. Arrows mark processes of Bergmann glial cells.

**f.** Vermis of a 21-day-old rat, in which immunostaining is restricted to the molecular layer (ML). The definitive granular layer (GL) and the medullary layer (M) are not stained. An identical staining pattern is present in the cerebellum of adult rats (not shown).

a, x 60; b, x 370; c, x 40; d-f, x 100
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recognition processes during morphological differentiation of certain brain regions. In the embryonic CNS of the mouse, CD15-carrying glycolipids are mainly found on proliferating neural cells of the ventricular and subventricular zone of the cerebral cortex, whereas migrating or postmigratory cells are not labelled (Yamamoto et al., 1985). During postnatal development of the rat retina, CD15 immunoreactivity is detectable in the differentiating neuroepithelial layer and in the inner plexiform layer (Fig. 7), when synaptogenesis of the ganglion cell dendrites with processes of amacrine cells occurs (Raedler and Sievers, 1975). During the postnatal development of the rat cerebellar vermis maximal immunoreactivity of CD15 is found within the inner granular layer during the second postnatal week (Fig. 8), when the vertical migration of the granular cells is most vigorous (Altman, 1969, 1972). At the end of the migration process, which is at
the 3rd postnatal week, the staining of CD15 is hardly detectable anymore. This finding suggests that the CD15 epitope favors the settlement of granule cells. During development of the rat spinal cord, CD15 is expressed by roof plate glia, and it has been assumed that the molecule may attract sensory axons (Snow et al., 1990). A similar mechanism of targeting cells into a particular area has been proposed for other cell adhesion molecules, such as N-CAM and N-cadherin (Rutishauser and Jessell, 1988; Takeichi, 1988; Edelman and Crossin, 1991). In the prospective white matter of the rat cerebellum, transient CD15 immunoreactivity is detectable presumably on unmyelinated axons during the first and second postnatal week with its maximum at the 5th day (Fig. 8c). During this period, differentiation of oligodendrogial cells is most extensive with the first appearance of myelin basic protein at day 5 (Reynolds and Wilkin, 1988). In line with these data, it seems possible that CD15 on axonal surfaces participates in axonal-oligodendrocyte contacts during myelination. In the human brain the carbohydrate determinant may be involved in myelin maturation. In the white matter of human cerebellar hemispheres, the molecule is first discernible in the cytoplasm of young oligodendrocytes during myelination. It is well conceivable that CD15 participates in the maturation process of oligodendrocytes in concert with other sequentially-expressed marker antigens (Cameron and Rakic, 1991; Goldman and Vaysse, 1991; Hardy and Reynolds, 1991).

In the human cerebellum, CD15 is transiently expressed on the outgrowing parallel fibers (PF), during their synaptogenesis with Purkinje cell dendrites (Gocht et al., 1992). Within the three subdivisions of the cerebellum, i.e. hemispheres, vermis, and the flocculonodular lobe, the CD15 expression in PF follows a different timing of morphogenesis. Thus, diminution of immunoreactivity occurs first in the phylogenetically oldest part, the flocculonodular lobe, then in the vermis and finally in the hemispheres. Additionally, adjacent areas in the hemispheres exhibit different rates of maturation, which is reflected by different intensities of CD15 immunoreactivity in the PF (Fig. 9a,b). Remarkably, during cerebellar development fading of PF labelling takes place in a graded fashion, that is, waning first starts in the deep layers of PF originating from the earliest migrating granule cells, and then progressively extends towards the superficial layers of the PF, which are derived from the latest migrating granule cells (Rakic, 1972; Sidman and Rakin, 1973; Hirano, 1983) (Fig. 9). Functionally, CD15 may act as a pathfinding molecule in growing PF, e.g. in fasciculation of the axons, as it is known for other neuronal determinants, such as Ng-CAM, L1, and TAG-1 (Fischer et al., 1986; Hoffman et al., 1986; Furley et al., 1990; Edelman and Crossin, 1991). CD15 is also transiently expressed in the neurons of the developing human dentate nucleus, where it is present from the 32nd week of gestation until the 15th postnatal month (Gocht et al., 1992). During this period of differentiation, CD15-positive neurons diminish in numbers with increasing age. It is possible that CD15 is involved in the organization of fiber input into the dentate nucleus, i.e. from Purkinje cell axons, mossy and climbing fibers or output projections towards the red nucleus and thalamic nuclei.

All the above outlined examples indicate that CD15 functions as a guiding molecule which directs cell migration. Recently, it has been shown that CD15 may also have repulsive effects on outgrowing axons in the mouse optic system (Marcus et al., 1995). During the outgrowth of retinal axons, CD15 is expressed in a thin raphe at the optic chiasm where ventrotemporal axons turn away and remain uncrossed. Thus, it seems possible that CD15 exerts a dual function during CNS development, on the one hand attracting axons as a growth-promoting molecule and on the other hand playing an inhibitory role in forming barriers for growing axons. A possible explanation for these contradictory functions of CD15 could be that different ligands may bind to the carbohydrate moiety, which during development are differentially expressed.

Abnormal CD15 expression in brain diseases

Abnormally high concentrations of CD15 have been described in some malignant non-neural tumors, such as carcinoma of the colon, kidney, mammary gland and in lymphomas (Fox et al., 1983; Hansson et al., 1983; Hsu and Jaffe, 1984; Shi et al., 1984; McCarthy et al., 1985; Wieczorek et al., 1985; Itzkowitz et al., 1986; Sewell et al., 1987; Yuan et al., 1987; LeBrun et al., 1992).

In human gliomas varied staining patterns for CD15 may occur. Budka and Majdic (1985) find intense decoration of tumor cells in astrocytomas and oligodendrogliomas, regardless of their differentiation using the antibody VIM-C6 in frozen sections. However, in a larger series of brain tumors embedded in paraffin and stained with MMA antibodies, Reifenberger and co-workers (1992) describe that most low grade gliomas reveal a weak to moderate staining intensity, whereas anaplastic tumors are constantly negative for CD15. In contrast, reactive astrocytes at the border of the neoplastic lesions are strongly stained with antibodies against CD15. We have observed that on the contrary to gliomas, primary medulloblastomas are always negative for CD15, but recurrences constantly express CD15, which is not related to astrocytic differentiation in these tumors (Fig. 10a,b). During the consecutive appearance of recurrences, the intensity of CD15 neo-expression seems to increase rendering this carbohydrate a prognostic indicator, as has already been suggested for premalignant colon polyps (Yuan et al., 1987), papillary thyroid (Schröder et al., 1987), and colonic carcinomas (Taki et al., 1988). Similarly, strong immunostaining is found on the cell surface and/or in the cytoplasm of reactive astrocytes in freshly demyelinated lesions of
Fig. 9. Developmental patterning of CD15 in the parallel fibers of the human cerebellum. 

a. 27-week-old male fetus. Section through the quadrangular lobule. Faint immunoreactivity is found within the molecular layer (ML); note that the lamina dissecans (LD) is still present. Slight counterstaining with hemalum. x 380.

b. 27-week-old male fetus. Section through the biventral lobule, where the lamina dissecans has disappeared. Parallel fibers in the molecular layer here are strongly labelled. Note the relatively thick outer granular layer covering the molecular layer. Slight counterstaining with hemalum. x 380.

c. Biventral lobule from a 4-month-old girl. Parallel fibers in the outer half of the molecular layer are CD15-positive. x 330.

d. Biventral lobule from an 11-month-old boy. Except for a small superficial portion (asterisk) parallel fibers are CD15-negative. Arrows point to labelled Bergmann glial processes. Note involution of the outer granular layer. x 160.

e. Biventral lobule from a 46-year-old woman. CD15 immunoreactivity of the parallel fibers is absent. Arrows indicate labelling of Bergmann glial processes. x 130. (Reproduced with permission of the Springer-Verlag from Gocht et al., 1992; Anat. Embryol. 186, 543-556, original figure 4).
central pontine myelinolysis (CPM), which are about two to four weeks of age (Gocht and Löhler, 1990). Remarkably, within these foci reactive astrocytes co-express vimentin and laminin, which are both transiently produced by early glial cells during normal CNS development (Liesi, 1985; Stagaard and Möllgård, 1989; Gocht et al., 1992). However, reactive astrocytes in recent CPM lesions are only weakly labelled with antibodies to GFAP. Conversely, in several months old CPM foci astrocytes forming a dense fibrillary gliosis are only faintly stained for CD1.5, whereas hypertrophic astrocytes at the margin of the lesions strongly express CD1.5. A similar staining pattern is observed in other non-neoplastic brain lesions, such as multiple sclerosis and subtotal ischemic alterations, in which again fresh lesions contain strongly CD15-immunoreactive astrocytes and old foci are filled with weakly-stained fibrillary astrocytes (Gocht, 1992b). In crushed-induced traumatic lesions of the optic nerve of adult rats the site of injury contains intermediate filament-bearing glial cells, the cytoplasm of which is stained with antibodies to CD15 (Fig. 11), whereas no GFAP labelling is detectable (Gocht, 1992b; Gocht and Löhler, 1993). These cells could represent early astrocytes, which may express other intermediate filaments apart from GFAP (Dahl et al., 1981; Fedoroff et al., 1983). A similar abnormal cytoplasmic distribution of CD15 has been found in carcinoma of the kidney, mammary gland, stomach and colon (McCarthy et al., 1985; Sewell et al., 1987; Ohtani et al., 1991). Normal epithelial cells of these tissues disclose plasma membrane staining with antibodies against CD15, whereas corresponding carcinoma cells may accumulate the carbohydrate in their cytoplasm. Strongly CD15-stained reactive astrocytes also occur in the dysmyelinated CNS of the myelin deficient (md) rat mutant (Gocht and Löhler, 1993), which suffers from a point mutation in the proteolipid protein (Boison and Stoffel, 1989). In other studies it has been demonstrated that reactive astrocytes in «white matter» tracts of the md mutant exhibit immature phenotypes (Cammer and Tansey, 1989; Friedman et al., 1989; Rohlmann et al., 1992).

Fig. 10. CD15 immunoreactivity in a medulloblastoma of a 7-year-old boy, who suffered from two recurrences of this neuroectodermal tumor. No immunostaining is observed in the primary tumor (a), while numerous tumor cells of the second recurrence exhibit strong CD15 labelling (b). x 370
CD15 immuno-reactivity within the lesion site of the optic nerve of 40-day-old rats, 6 days after crush injury.

a. Light microscopically intracytoplasmic staining is found in glial cells. X 550.

b. Ultrastructurally, reaction product is visible in the cytoplasm of a double-nucleated cell, which represents an astrocyte. X 13,000.
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Taken together, up-regulation of CD15 in concert with re-expression of other onco-fetal antigens in reactive astrocytes could reflect increased cellular activities in attempted tissue repair. The importance of CD15 to form intercellular contacts is also obvious from the investigations of malignant brain tumors. At the border of the tumors reactive astrocytes that have lost their normal cellular contacts enhance their expression of CD15, whereas the tumor cells themselves possibly have lost their ability to form efficient cellular contacts.

Putative growth-inhibiting properties of CD15 during CNS regeneration

The failure of axons of the CNS to functionally regenerate is mainly due to inhibition by surrounding glial cells, i.e. oligodendrocytes and astrocytes (see review by Schwab et al., 1993; Bahr and Bonhoeffer, 1994; Fawcett, 1994; Sivron and Schwartz, 1994). The hypothesis that oligodendrocytes and central myelin strongly inhibit axonal regrowth is supported by the observation that in the almost myelin-free optic nerve of wildtype (Marciano et al., 1990; Gocht and Löhrer, 1993). Interestingly, within the lesion site of injured wildtype optic nerves, astroglia-like cells are present which contain CD15-positive reaction product in their cytoplasm (see Fig. 11) (Gocht and Löhrer, 1993). In contrast, the area of tissue necrosis in md optic nerves remains CD15-negative, although glial cells bearing intermediate filaments can be readily demonstrated. Thus, it may be possible that CD15-positive glial cells exert growth-inhibiting properties. This assumption is in line with the observation by Santos-Benito et al. (1992) that a synthetic carbohydrate compound containing the CD15 epitope inhibits the proliferation of neuroblastoma cells in vitro. Moreover, the growth-repressive effect of CD15 on outgrowing axons has also been recently demonstrated in the mouse optic system (Marcus et al., 1995).

CD15 is involved in cellular adhesion and signal transduction

The initial experiments by Solter and Knowles (1978) suggest that CD15 may act as cell adhesion molecule on the cell surface of preimplantation mouse embryos during compaction. When fully compacted embryos at the 8 to 16 cell-stage were incubated with free CD15-containing oligosaccharides, decompaction occurred (Bird and Kimber, 1984; Fenderson et al., 1984). Additional experiments imply that at least one recognition process of embryonic cells mediated by CD15 is a homophilic binding mechanism, i.e. it is based on CD15-CD15 interactions (Eggens et al., 1989; Fenderson et al., 1990). On the other hand, CD15 may be involved in a heterophilic CD15-selectin binding process (Larsen et al., 1990), as has been shown for leukocyte-endothelial cell adhesion (Springer and Lasky, 1991; Kerr and Stocks, 1992). Activated endothelial cells, e.g. at sites of inflammation, express platelet activation-dependent granule-external membrane protein (PADGEM) on their surface (McEver et al., 1989) which belongs to the P-selectin family. Neutrophil granulocytes presenting CD15-containing glycoconjugates on their surface could adhere to endothelial cells via a CD15-P-selectin interaction followed by extravasation into the surrounding inflamed tissue. Moreover, activated platelets can bind to neutrophils and monocytes via a PADGEM-CD15 binding mechanism (Larsen et al., 1990).

Other studies, which were aimed at analyzing the functional properties of CD15 in leukocytes, included incubation of myeloid cells in the presence of anti-CD15 antibodies, which are believed to act as ligands of CD15-containing receptor systems. These experiments demonstrate that ligand binding to CD15 may alter several functional activities of granulocytes, such as suppression of phagocytosis, increased migration, increased adhesion to endothelial cells, inhibition of chemotaxis, cell aggregation associated with degranulation, flattening, and superoxide generation (Nauseef et al., 1983; Melnick et al., 1985; Buescher et al., 1989; Forsyth et al., 1989; Lund-Johansen et al., 1992; Harvath et al., 1995; Ingerpuu et al., 1995). Interestingly, CD15 seems to be associated with protein kinases and anti-CD15 antibodies induce tyrosine phosphorylation in monocytes, indicating that the trisaccharide may be involved in signal transduction processes (Angelisova et al., 1995; Ball, 1995).

The presence of CD15 at distinct cellular sites of neurons and glial cells also implies a peculiar functional specialization of the carbohydrate in the CNS. The occurrence of CD15 on the plasmalemma suggests an adhesion function in glial cells (Niedeck and Löhrer, 1987; Gocht, 1992b; Gocht et al., 1994) and in neuronal processes to fasciculate elongating axons during development (Gocht et al., 1992). Furthermore, CD15-containing molecules at the outer surface of glial and neuronal cells may act as receptors for signal transduction processes, which serve to maintain the neural integrity in the mature state and to control cell sorting during development. However, the occurrence of CD15 in the cytoplasm of glial cells and neurons suggests that the carbohydrate may also be involved in intracellular transport mechanisms. In general, cytosolic glycoconjugates may serve as recognition markers, which are coupled to specific proteins, e.g. enzymes. These carbohydrate-labelled proteins could then be targeted to specific intracellular compartments via their binding to endogenous lectins (for review see Kornfeld, 1986, 1987; Hart et al., 1989). Up to now, the subcellular compartments containing the CD15-synthesizing glycosyltransferases are not known. Thus, it is conceivable that CD15, after being produced in certain cell types, may be released and taken up by other cells, whereas the carbohydrate is utilized for specific cell functions. That in fact CD15 can be actively shed by glial cells is observed in mixed astroglial and oligo-
dendroglial cell cultures, where CD15 immunoreactivity is detectable on the surface of the culture dishes (Löhler and Niedieck, unpublished observation).

**Future perspectives**

Until now, we have accumulated various data pertinent to putative functions of CD15 in the CNS, but currently, results from functional assays are still lacking. Future experiments will be aimed at assessing the role of this trisaccharide in tissue organization processes by use of 

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Future perspectives

Until now, we have accumulated various data pertinent to putative functions of CD15 in the CNS, but currently, results from functional assays are still lacking. Future experiments will be aimed at assessing the role of this trisaccharide in tissue organization processes by use of *in vitro* and *in vivo* perturbation experiments with specific blocking ligands. Moreover, the demonstration of natural ligands of CD15 in the CNS will help to clarify the mechanisms of cell interactions in the normal and altered brain. Another major task will be the analysis of the *in situ* localization of CD15-synthesizing glycosyltransferases in mature and immature cells and to follow possible translocations of the carbohydrate epitope into subcellular compartments. Further investigations should focus on pathological situations, in which altered functions of CD15 may explain their pathogenesis and prognosis; for example the potential of neoplastic cells to invasively grow and metastasize. The cloning of DNA sequences, which encode CD15-specific glycosyltransferases will further offer the opportunity to modify the expression of CD15 in distinct cells and to study their fate during development.

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