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NEURAL CELL ADHESION MOLECULES*

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Adhesion molecules are expressed on the surface of various cells and establish cell - cell interaction, playing important roles in development, inflammatory reaction, immune response, and tissue regeneration. Neural adhesion molecules, found on neurons or glial surfaces, are involved in the migration of neurons, neurite formation, myelination, and denervation - reinnervation. The roles of cell adhesion molecules in malignancies, normal and abnormal development and as receptors in viral infections, constitute major fields of research and may have important diagnostic and therapeutic implications. *Key words: adhesion molecule, integrin, neural cell adhesion molecule, immunoglobulin superfamily.*

Cell - cell interaction is necessary for the development of multicellular organisms. Embryogenetic and histogenetic events, i.e., the migration of embryonic cells, their localization, and the transfer of information between them is made possible by cellular adhesion and recognition. The discovery of cellular adhesion molecules on the surface of various cells and of extracellular matrix proteins in the tissue matrix, while opening a vast field of research, has allowed scientists to better understand the basic principles of development, the mechanisms of immune response, inflammatory reaction, and tissue regeneration[1].

According to its structure, an adhesion molecule may be considered in one of two major groups: 1) the immunoglobulin superfamily, and, 2) the integrin family[2]. Neural adhesion molecule (NAM)'s, which are found on neurons, glial cells and sometimes in other tissues, generally belong to the first group.

Different NAM's are expressed on the cell surface at different stages of development. Moreover, one cell type may have more than one NAM at one time[1]. While two adhesion molecules may cooperate in some locations, they can antagonize each other in some other tissues. The result (i.e., embryogenesis, inflammatory reaction) depends on the type and the quantity of the molecules that are expressed on each group of cells.

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Most of the studies concerning NAM's are done on animals, especially chicken and rat embryos. The structure of these molecules is evolutionally conserved. The early postnatal cerebellum has been the tissue preferred in the study of NAM's; the main reason is the well known morphology and easy accessibility of this organ, and, particularly, the cell migration that occurs during its development and involves the adhesion molecules. Histologically, proliferating premigratory granule cells are first observed in the outer part of the cerebellar granular layer; then these cells, now postmitotic, associate with the Bergmann glial cell processes, forming parallel fibers in the molecular layer. The granule cell body then migrates to the internal layer along these processes where it takes its final position. The important function adhesion molecules have in this process has provided scientists a good model to examine them.

Before their role in normal and pathological situations, the main characteristics of the NAM's will be considered below.

Neural cell adhesion molecule (N - CAM) : This molecule, expressed on early embryonic cells, has been purified from embryonic and adult chicken brains[3]. It is also present on adult brain neurons, glia, muscle, heart, intestine, kidney and lens. N - CAM establishes cell - cell adhesion by a homophilic mechanism, i.e., the N - CAM molecule on one cell binds to the N - CAM of the other[4]. It is a complicated molecule; it has embryonic and adult forms, the latter differing from the former by the lack of polysialic acid, therefore, by molecular weight, and also, by an increased attaching capacity. The two forms occur at different rates in different brain regions and have a role in neuron - neuron, neuron - glia and glia - glia relations. In the peripheral nervous system, N - CAM is involved in Schwann-axon and Schwann - Schwann interaction.

Neuronal - glial adhesion molecule (Ng - CAM) : This molecule, although structurally and immunologically related to N - CAM (with which it shares at least one antigenic determinant), has distinctive properties[5]. It is called a secondary cellular adhesion molecule because it is expressed on more mature (postmitotic) neurons, especially axons, and Schwann cells. It is involved in neuron - neuron and neuron - glia interaction, particularly in neuronal migration, and has been shown on cerebellar granule cells just before their migration. It is not expressed on glial cells, therefore, the mode of action of Ng - CAM is homophilic for neurons, but heterophilic for neuron - glia interaction. The molecule it binds on, astroglia, is still to be identified. The probable mammalian equivalent of Ng - CAM is nerve growth factor - inducible large external glycoprotein (NILE) which has been shown on the PC12 pheochromocytoma cell line[6].

L1 : This molecule is present on unmyelinated fasciculating axons and Schwann cells and is involved in interaction between these elements. It disappears after the completion of myelination. Antibodies to L1 prevent the neurite formation of

Schwann cells[7]. L1 also has a role in the migration of cerebellar granule cells to the internal granular layer. L1, Ng - CAM and NILE have similar immunological and structural properties[8].

Myelin - associated glycoprotein (MAG) : MAG is found around the axons. It is first detected in the oligodendrocytes, then on their surface during the ensheathing of axons by these cells[9]. It may be involved in the pathogenesis of some polineuropathies. In 40 percent of patients with peripheral neuropathy associated with monoclonal IgM, the IgM reacts with MAG[10].

Adhesion molecule on glia (AMOG) : This is a recently discovered molecule that is involved in neuron - astrocyte adhesion and cerebellar granule cell migration[11].

Some other adhesion molecules in the immunoglobulin superfamily are Po (on peripheral nerves), contactin, carcinoembryonic antigen (CEA), intercellular adhesion molecule - 1 and 2 (ICAM - 1 and 2), CD4 (human immunodeficiency virus receptor), and poliovirus receptor. It is probable that new ones will be added as research in this field is pursued.

Liver - CAM (L - CAM) is the major adhesion molecule of the integrin family. This group differs from the first one in terms of structure and binding mechanism (calcium - dependent vs. calcium - independent). Several other molecules resembling L - CAM have been identified: N - cadherin, A - CAM, P - cadherin, T - cadherin, cell CAM 120/80, ARC - 1, etc. They have common points, such as 50 - 80 % identical aminoacid sequences, are all synthetized as large precursor molecules, have 3 - 4 internal repeats and distinct distribution in adult tissues. As shown in animal studies, N - cadherin is known to play a role in the migration of neural cells.

The role of NAM's in development : Because of the interesting events occurring during its development, namely the migration of granular cells, the cerebellum has been an organ preferred by scientists in order to examine the roles of NAM's. The administration of antibodies to different NAM's in experimental conditions constitutes a valuable tool to prove the role of these molecules during development.

N - CAM is present in the developing cerebellum at all times. Ng - CAM is expressed in granule cells just before their migration and disappears later. Anti - N - CAM given to embryonic chicken does not cause significant impairment of cerebellar development. On the other hand, anti - Ng - CAM arrests the migration of granular cells at the external layer. Antibodies to cytoactin, an extracellular matrix protein, stop these cells at the molecular layer, implicating a role for cytoactin at a later developmental stage[12]. Anti - N - CAM, injected into the retina of chick embryos, inhibits the development of visual pathways. The density and the structure of NAM's change during development. In mice and

chicks the concentration of N - CAM is highest in the perinatal period. The conversion of the embryonic to adult form, which involves a change in molecular weight and structure, occurs at different times in different areas of the brain, implicating a role for morphogenesis[13].

Pathological conditions and NAM's : It is now well-established that N - CAM changes in amount and location in relation to denervation and reinnervation. In normal muscle, N - CAM is found in the interstitium. In peripheral nerve injury, it increases in areas which were synapses before the denervation. When reinnervation is complete, N - CAM returns to the baseline amount. In cases of chronic denervation, it remains at high levels[14]. Similar findings were shown in mixed cultures of neurons and Schwann cells. When neurons are taken off the culture medium, L1 and N - CAM increase on the surface of Schwann cells. This event may be mediated by neural growth factor (NGF) which is known to increase the synthesis of N - CAM in culture. These observations show that while N - CAM's affect the neurons, their location and their interactions with other cells, they also are influenced by them[15].

Failure of the normal conversion of embryonic N - CAM to the adult form has been associated with cerebellar histological abnormalities and clinical ataxia in the staggerer mutants of mice[1].

Another interesting and highly significant observation is the changes of adhesion molecules in malignancies or virally infected cells. Brackenbury et al[16] have shown a decrease in N - CAM expression and increase in motility in retinal cells transformed by rous - sarcoma virus. Some adhesion molecules are found on tumor cells, for instance, human mammary tumor cells express cell CAM 120/80.

One of the important discoveries about adhesion molecules has been their role as viral receptors. It has been established that poliovirus and human immunodeficiency virus use adhesion molecules in order to attach to cells. The most recent report on this subject involves the rhinovirus receptor, ICAM - 1[17].

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