[Frontiers in Bioscience 8, d357-359, January 1, 2003]

NEURAL CELL ADHESION MOLECULES – BRAIN GLUE AND MUCH MORE !

Michael Hortsch

Department of Cell and Developmental Biology, University of Michigan Medical School, Ann Arbor, MI 4809-0616, USA

TABLE OF CONTENTS

1. ABSTRACT

The formation of stable cell contacts is of pivotal importance for every metazoan life form. It is therefore not surprising that adhesive molecules appeared early during the evolution of multicellular organisms. The pioneering work of Johannes Holtfreter and others indicated that adhesive molecules, which reside in the plasma membrane on the surface of most cells, are not only important for establishing general cell adhesion and cellular contacts, but also convey a specific tissue and cellular identity to their host cells (1). Over the last few decades a large number of cell adhesion molecules (CAMs) have been identified and further characterized, and we have learned that the expression of these proteins is highly choreographed in terms of timing and cell identity.

2. INTRODUCTION

The majority of neural CAMs are composed of a surprisingly limited number of structural protein motifs, *e.g.*, immunoglobulin, fibronectin type III, cadherin, cholinesterase-like and semaphorin domains (Fig. 1)(2), so that most neural CAMs can be assigned to larger gene superfamilies. Individual members within each gene superfamily differ from each other by the number and the arrangement of these structural protein motifs, which delineate smaller subgroups or gene families. Some of these subgroups existed as separate gene families early during the evolution of the metazoan kingdom, *e.g.*, the L1 and the NCAM gene families (Figure 1) (3).

Organisms with simpler nervous systems usually contain in their genome only one, or just a few, representatives of each CAM gene family. However, species with more complex neuronal architectures have typically evolved an increasing number of CAM genes, many of which appear to have been generated by gene duplication events. This tendency towards multiplicity resulted not only in molecular redundancy for certain neural CAM functions, but also enabled the development of novel protein-protein interactions and the adaptation of additional developmental roles (4).

Few completely novel CAM structures have appeared over the last 600 million years of evolution. Even when new developmental processes and strategies have been adopted for the construction of more efficient and complex nervous systems, the CAMs involved in these novel processes usually belong to one of the already existing CAM gene superfamilies. For example, myelination of axonal extensions appears to be restricted to the chordate lineage and no β-subunits of voltage-gated sodium channels have been identified in invertebrate species. Nevertheless, both the β-subunits of mammalian voltage-gated sodium channels, as well as the CAMs associated with myelinated axons, are all members of the immunoglobulin gene superfamily that is also found in invertebrates and exhibit structural and functional similarities to evolutionary older CAMs.

In no other organ or tissue is the specificity of cellular contacts and the interaction between different cell types more complex and more important than in the nervous system. However, most neural CAMs, with the exception of the β-subunits of the voltage-gated sodium channels, do not participate in the major function of the mature nervous system, the conductance of electric signals. Rather they are involved in the development of the nervous system and are important during regeneration after nerve injury. As a result, many so-called “neural CAMs” are also expressed outside the nervous system, where they play similarly important roles in the development and maintenance of other tissues and organs.

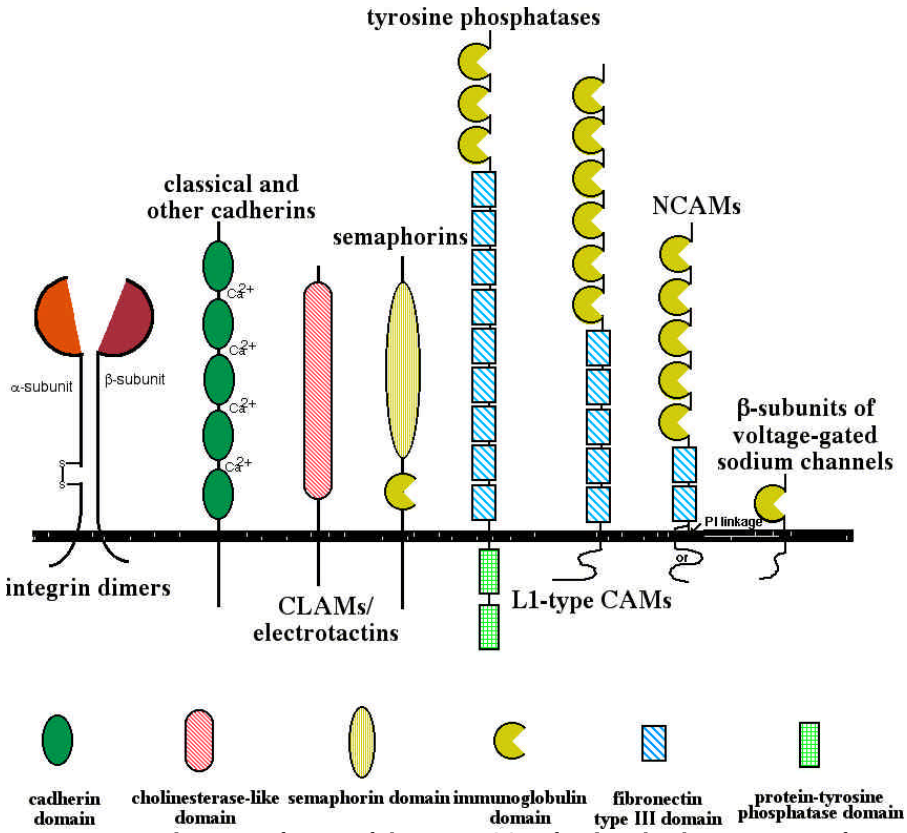

Figure 1. Shown are prototypic diagrams of some of the major CAM families that have important functions in the nervous system. Within each gene family individual members might vary in the exact number and the arrangement of the structural protein domains. As indicated for NCAM, differential splicing of primary transcripts might also generate additional protein isoforms from individual CAM genes.

As first formulated in Sperry's chemoaffinity hypothesis, neural CAMs are centrally involved in axonal pathfinding, target selection and synapse formation (5), but we have realized since 1963 that the mechanisms responsible for axonal pathfinding and neuronal target choices are far more complex than simple differences in neuronal adhesiveness. These behaviors are the result of integrating multiple molecular adhesion systems and also include diffusible factors and repulsive forces, such as netrins and semaphorins (6, 7). In addition, several axon guidance molecules, *e.g.*, some members of the semaphorin gene family, appear to have a dualistic nature. Depending on the circumstances (location and time of development) they can act either as adhesive or as repulsive molecules (8).

Axonal pathway and target choices and neuronal migration patterns are executed with extremely high fidelity during the development of the nervous system and result in a very reproducible and predictable cellular organization. The specificity of the cellular interactions that guide these processes is therefore of the utmost importance. Whereas some CAMs only interact with their own, identical type of CAM (homophilic adhesion), others only bind ligands different from themselves (heterophilic adhesion) and yet another group of CAMs uses both mechanisms of adhesion. Whereas many neural CAMs have strict and very narrow ligand specificities, others interact with a multitude of ligands, which are either expressed extracellularly or on the surface of other cells (trans-interactions) or within the same plasma membrane plane (cis-interactions). It appears that both the restricted specificity of some CAMs, as well as the ligand promiscuity of other CAMs, enables neurons to make the correct decisions in a changing cellular environment.

Although these adhesive functions are central features of all CAM families, most CAMs play important additional roles in the nervous system beyond their function as "cellular glue". Neural CAMs are often involved in maintaining the general structure of neurons and other nervous system cells and some even influence cellular differentiation and metabolic processes, including neural gene expression patterns. The structural aspect of neural CAM functioning is underscored by the fact that most adhesion proteins maintain connections with elements of the cytoskeleton. Often these intracellular interactions are regulated by the extracellular adhesive status of the CAM, and vice versa. This provides a direct link between neural cell adhesion and overall cellular organization.

Since most neural CAMs do not contain an intrinsic enzymatic activity (with the exception of tyrosine phosphatases), until recently the involvement of CAMs in

cellular signaling processes has neither been recognized nor sufficiently appreciated. The first indication that CAMs are profoundly involved in such processes came from *in vitro* observations that many neural CAMs are potent inducers of neurite outgrowth or, as in the case of semaphorins, induce growth cone collapse and axonal repulsion. A wealth of genetic, pharmacological and molecular data now indicates that many neural CAMs directly or indirectly modulate several classical cellular signaling pathways (9).

Considering the central involvement of CAMs in many developmental processes of the nervous system, it comes as no surprise that mutations in many neural CAM genes are often lethal or cause a range of neurological phenotypes (10). These phenotypes may range from severe structural malformations of the brain or other parts of the nervous system, defects in the myelination of axons, uncoordinated motor behavior due to insufficient innervation of muscles, to mental retardation and other cognitive failures. Mutations in neural CAM genes have been identified as the molecular defect in a growing number of mouse mutations and human genetic syndromes with neurological phenotypes. Although many of these mutations that have been cloned and further characterized from affected human individuals result in the complete loss of CAM function, they often do not cause an embryonic lethal phenotype (11). It is tempting to speculate that paralogous gene products in mammalian species may partially compensate for the lack of a specific CAM protein (4). In support of this hypothesis, mutations in the single representative of a CAM gene family are often lethal in the fruit fly *Drosophila*, whereas the deletion of just one of several paralogous genes in mammalian species rarely causes embryonic death. The further analysis of these mutations in various CAM genes and their phenotypes will contribute to our understanding of many developmental processes within the nervous system and potentially in other organs and tissues, as well.

Most articles in this special issue on "Neural Cell Adhesion Molecules" focus on one specific family or group of CAMs, which share structural similarities. The authors discuss not only the structural variations within each gene family, but also the functional aspects, individual protein-protein interactions, developmental processes and mutation phenotypes that are associated with members of each group of adhesive molecules. In addition, several reviews address the functional involvement of neural CAMs in specific cellular or developmental processes, such as signal transduction or myelination. Although many of the major CAM families are known to be crucial players in developmental processes in the nervous system (integrins, immunoglobulin domain CAMs, cadherins and others), several novel groups of adhesive molecules have been only recently identified to have important functions in the nervous system, *e.g.,* leucine-rich repeat and synaptic CAMs. Reviews describing these new neural CAMs will be added to the special issue on "Neural Cell Adhesion Molecules", when more information on their structure and their function is available. Much more work is left to be done before we will fully understand the functional roles and the importance of adhesive processes in the nervous system and the molecules that mediate them.

3. ACKNOWLEDGEMENTS

I would like to thank my colleagues Drs. Kristen Verhey and Pamela Raymond for their helpful comments on the various drafts of this manuscript. Research in my laboratory is supported by grants from the National Institute of Child Health and Human Development and the Developmental Neuroscience Program of the National Science Foundation.

4. REFERENCES

1. Townes P. L. & J. Holtfreter: Directed movements and selective adhesion of embryonic cells. *J Exp Zool* 128, 53-120 (1955)

2. Chothia C. & E. Y. Jones: The molecular structure of cell adhesion molecules. *Annu Rev Biochem* 66, 823-62 (1997)

3. Grenningloh G., A. J. Bieber, E. J. Rehm, P. M. Snow, Z. R. Traquina, M. Hortsch, N. H. Patel & C. S. Goodman: Molecular genetics of neuronal recognition in *Drosophila*: evolution and function of immunoglobulin superfamily cell adhesion molecules. *Cold Spring Harb Symp Quant Biol* 55, 327-40 (1990)

4. Hortsch M.: Structural and functional evolution of the L1-family: Are four adhesion molecules better than one? *Mol & Cell Neurosci* 15, 1-10 (2000)

5. Sperry R. W.: Chemoaffinity in the orderly growth of nerve fiber patterns and connections. *Proc Natl Acad Sci USA* 50, 703-10 (1963)

6. Yu T. W. & C. I. Bargmann: Dynamic regulation of axon guidance. *Nat Neurosci* 4 Suppl, 1169-76. (2001)

7. Mueller B. K.: Growth cone guidance: first steps towards a deeper understanding. *Annu Rev Neurosci* 22, 351-88 (1999)

8. Van Vactor D. V. & L. J. Lorenz: Neural development: The semantics of axon guidance. *Curr Biol* 9, R201-4 (1999)

9. Walsh F. S. & P. Doherty: Neural cell adhesion molecules of the immunoglobulin superfamily: Role in axon growth and guidance. *Ann Rev Cell Dev Biol* 13, 425-56 (1997)

10. Kamiguchi H., M. L. Hlavin, M. Yamasaki & V. Lemmon: Adhesion molecules and inherited diseases of the human nervous system. *Annu Rev Neurosci* 21, 97-125 (1998)

11. Hortsch M.: The L1 family of neural cell adhesion molecules: Old proteins performing new tricks. *Neuron* 17, 587-93 (1996)