STRUCTURE AND FUNCTION OF SOLUBLE NCAM

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INTRODUCTION

Specific nerve connections are generated by multiple steps in cell-cell interactions. These steps include cell proliferation, migration, aggregation, differentiation, synapse formation, cell death and elimination of synapses. Adhesive interactions between cell surfaces are of central importance during development of the nervous system. An understanding of the role of cell surfaces in cell recognition depends on the elucidation of the molecular mechanism involved. The neural cell adhesion molecule, NCAM, is presently the best characterized mammalian cell-cell adhesion molecule. NCAM has been shown to have a function in neuron-neuron, neuron-astrocyte and astrocyte-astrocyte adhesion (Rutishauser et al., 1976; Keilhauer et al., 1985), and in nerve-muscle cell recognition (Grumet et al., 1982).

NCAM mediated cell-cell adhesion occurs by a homophilic binding mechanism (Rutishauser et al., 1982), in which NCAM on the surface of one cell binds to NCAM on another cell. Cole et al. (1986) have shown that although NCAM mediated adhesion involves homophilic binding, the binding of cell surface heparan sulphate to NCAM is also required. The membrane associated forms of NCAM consist of three polypeptides which in SDS-polyacrylamide gels migrate with Mr's of ca.
The main difference between NCAM A and B is the size of their cytoplasmic domains (Gennarini et al., 1984; Nybroe et al., 1985; Murray et al., 1986). In contrast, NCAM C lacks a transmembrane domain (Nybroe et al., 1985) and is anchored in the membrane not by a stretch of hydrophobic amino acids, but by a phospholipid (He et al., 1986).

cDNA sequence data (Hemperly et al., 1986) indicate that NCAM is a member of the immunoglobulin gene superfamily. Members of this superfamily all share a common structure called the immunoglobulin homology unit. NCAM has probably at least four homology unit sequences, and it has been suggested (Hunkapiller and Hood, 1986) that the homophilic and polyvalent nature of NCAM may result from receptor-ligand binding analogous to the paired homology unit associations that generate the domain structure of other molecules of the superfamily.

Nearly all biochemical studies on NCAM have been performed on the membrane associated form. However, soluble forms of NCAM have been observed and quantified in human cerebrospinal fluid, amniotic fluid and serum (Jørgensen and Bock, 1975; Jørgensen and Nørgaard-Pedersen, 1981; Ibsen et al., 1983a). In cell culture supernatants the presence of NCAM was indicated by studies by Rutishauser et al. (1978) who produced antibodies against NCAM using chick retinal cell culture supernatants as source of antigen, and by Thiery et al. (1977) who were able to block the inhibitory effect of NCAM antibodies on cell-cell adhesion by means of soluble antigens from chick retinal cell culture supernatant. Schubert et al. (1983) showed that embryonic chick retinal cells release macromolecular aggregates, termed adherons, into their culture medium. Adherons promote cell-substratum attachment, and a polypeptide of apparent molecular weight (Mr) 170,000, immunochemically identical to NCAM, was demonstrated to be the cell-substratum adhesion molecule of the adherons (Cole and Glaser, 1986).