Investigation into the mechanisms underlying functionally important interactions of Neural Cell Adhesion Molecule.

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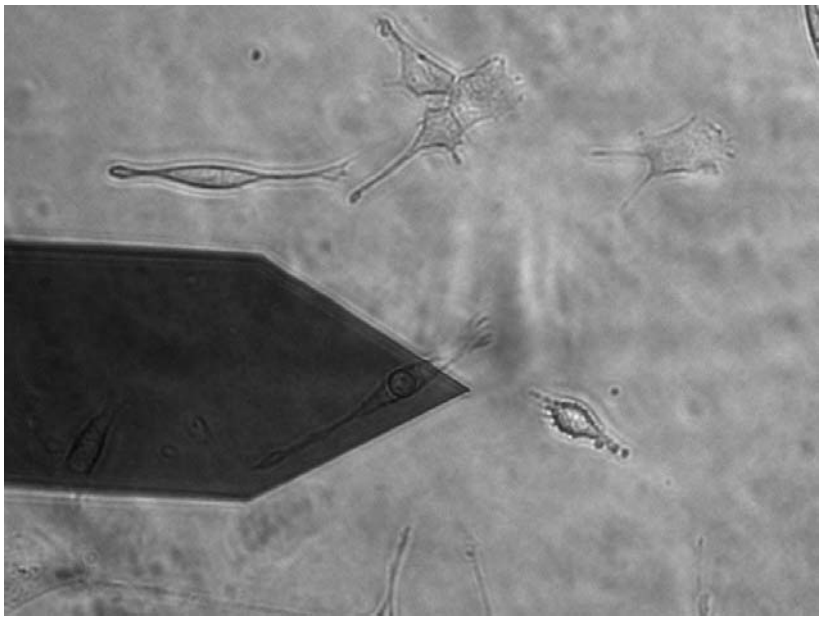

The neural cell adhesion molecule (NCAM) is a transmembrane protein with important roles in nervous system development and learning and memory (a). These roles depend on different interactions including NCAM homophilic binding to mediate cell-cell adhesion. NCAM can undergo multiple modifications including the addition of polysialic acid (a bulky negatively charged sugar). Another is the use of a small variable alternatively spliced exon (VASE), which introduces ten amino acids into NCAM.

NCAM-PSA promotes neuronal regeneration but decreases the adhesion strength of NCAM homophilic binding. Conversely, inclusion of VASE inhibits NCAM stimulation of neuronal regeneration (b). Shedding light on the mechanism for this and the overall function of VASE was the purpose of this investigation.

One possibility for VASE inhibition of regeneration is that it increases the adhesion strength of NCAM, in a reciprocal manner to PSA. To test this, the adhesiveness of NCAM and VASE has been determined in a physiological context using single cell force spectroscopy. Cells expressing either no NCAM, non-VASE NCAM or VASE were allowed to interact, then the force required to separate them was recorded. These experiments have clearly shown that two VASE interacting cells require a greater force to separate them than two non-VASE NCAM cells, indicating that VASE cells exhibit increased adhesion.

To determine if it is the homophilic binding strength of the VASE protein alone which accounts for the increase in cell adhesion, the individual proteins are being investigated using single molecule force spectroscopy. Understanding the mechanism of VASE may allow its inhibitory functions to be knocked down to permit nervous system regeneration.

(a) Maness, P. F., Schachner, M. Nat. Neurosci. 10, 19-26, 2007.
(b) Saffell, J. L. et al. J. Cell Biol. 125, 427-436, 1994.