Targeting Talk: Retrograde Transport

by Dr. Ronald G. Wiley

Q. I'm interested in using SAP to eliminate cells through retrograde transport, like OX7-SAP and IB4-SAP have been used. Can you explain how retrograde transport works and if it is possible for this to work with dermorphin-SAP? What determines whether a targeted toxin will be able to be used in retrograde transport?

A. Current evidence indicates that effective suicide transport agents undergo endocytosis at nerve terminals followed by retrograde axonal transport of the endocytic vesicles containing the toxin. Experiments using vincristine have shown that the retrograde axonal transport of suicide transport toxins utilizes the fast transport system (microtubules). However, it is not known what determines whether or not a specific toxin-ligand undergoes axonal transport after internalization.

Empirically, it has been observed that immunotoxins (OX7-SAP, 192-Saporin, anti-DBH-SAP) and lectin-toxins (ricin, volkensin, IB4-SAP) all undergo retrograde axonal transport and are therefore effective suicide transport agents. This is not true, however, for neuropeptide-toxin conjugates, such as dermorphin-SAP. For example, in an unpublished study, we injected large doses (1-2 µg) of dermorphin-SAP into the lumbar intrathecal space of rats. After 2-3 days, rats were sacrificed and lumbar dorsal root ganglia examined for evidence of toxin effect (striking chromatolysis). None was found after examining numerous ganglia and >15,000 primary afferent neurons. Apparently, dermorphin-SAP is not retrogradely transported even if it is taken into the primary afferent terminals that express the mu opioid receptor (MOR).

Q. If a targeted toxin cannot be used in retrograde transport, will it only kill cell bodies in the injection site or will it also kill terminals?

A. Current evidence suggests that applying dermorphin-SAP to the population of MOR-expressing neurons in the dorsal horn of the spinal cord results in destruction only of the neurons in lamina II and not the primary afferent terminals that also express MOR. This may be a general principle but it has not been tested in any other situation for dermorphin-SAP, nor have SP-SAP and SSP-SAP been evaluated for terminal uptake and suicide transport. Any saporin taken into a nerve terminal should not be toxic unless retrogradely transported to the cell body since there are no ribosomes (site of saporin action) or protein synthesis in the nerve terminal.

Suggested Reading:

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