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Direct Bi-Directional Dialogues Between The Nervous System And The Immune System in health and disease

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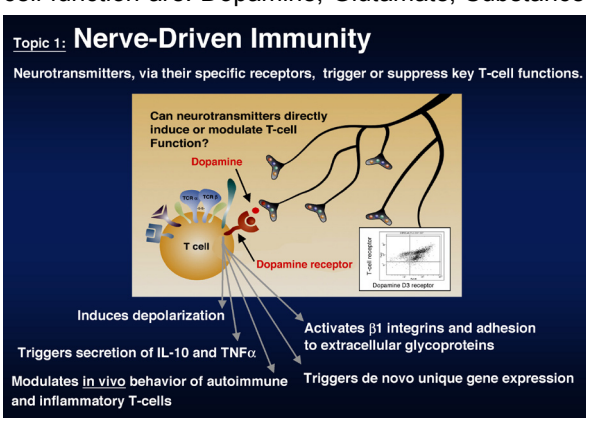
Topic 1. Nerve-driven Immunity: Neurotransmitters, through their specific receptors, trigger or suppress key T-cell functions (Fig 1):

Exploring the direct ways by which the immune, nervous and endocrine systems talk to each other holds great promises not only for a better perception of how the entire organism operates in health, but also for developing novel therapeutic strategies in various immunological and neurological diseases, among them autoimmune diseases, inflammatory diseases and cancers.

To explore the potential direct bi-directional dialogues between the immune and the nervous systems, we asked whether T-cells, alike neurons, express specific receptors for brain neurotransmitters, and if so, whether neurotransmitters secreted by nerve fibers, can by themselves trigger or suppress key T-cell functions. If so, we further investigate whether the T-cell activation/function triggered by a given neurotransmitter differs quantitatively or qualitatively from that triggered by "classical' T-cell activators alike antigens. So far, the neurotransmitters and neuropeptides studied for their direct effects of T-cell function are: Dopamine, Glutamate, Substance P, Calcitonin-gene-related-peptide, Neuropeptide Y, Somatostatin, GnRH-I and GnRH-II.



To this end, my collaborators and I made a series of observations, establishing that several potent neurotransmitters, by direct binding to their cognate receptors on the T-cell surface, can by themselves trigger or rather suppress highly important T-cell functions and features. Two examples are:

Functional glutamate receptors in human T-cells: We discovered for the first time that normal, cancer and autoimmune human T-cells, alike neurons, express high levels of ion-channel glutamate receptors of the AMPA subtype-3 (GluR3). Sequencing showed that the T-cell GluR3 is identical to the brain GluR3. Glutamate (10nM) by itself triggered several T-cell functions including integrin-mediated T-cell adhesion to laminin and fibronectin, a function normally performed by activated T-cells only. Glutamate also increased the CXCR4-mediated T-cell chemotactic-migration towards the key chemokine SDF-1. These findings could be of substantial scientific and clinical importance for normal neuroimmune dialogues, and to CNS diseases and injury, and especially to: a) T-cell transmigration to the CNS and patrolling in the brain, b) T-cell mediated multiple sclerosis

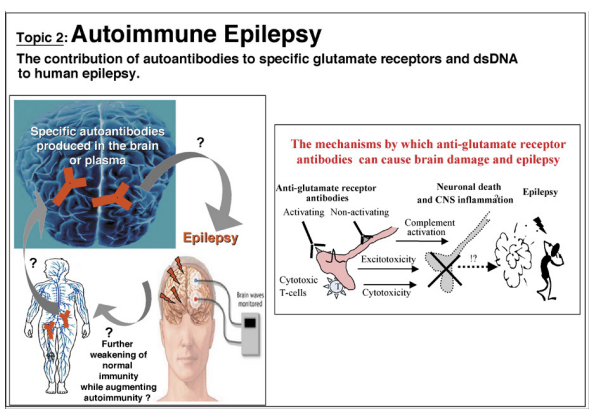
Functional Dopamine receptors in T-cells:

We discovered that human T-cells express on their outer membranes functional dopamine receptors of the D3 and D2 subtypes, and that dopamine by itself triggers important T-cell functions, among them (Fig 1) adhesion to fibronectin and laminin, cytokine secretion of inflammatory and anti-inflammatory cytokines, and gene expression. These findings may be of substantial importance for understanding and treating various neurological and immunological diseases associated with either excess or lack of dopamine, or with insufficient or deleterious T-cell functions.

Topic 2: Autoimmune Epilepsy:
The contribution of autoantibodies against specific glutamate receptors and against dsDNA to human epilepsy (Fig 2).

1-2% of the world population suffers from epilepsy of various types. Frequently, the etiology is completely unknown, and 20-30% of epilepsy patients do not respond to any medication, thus suffering from recurrent seizures and constant danger. Traditionally, epilepsies have been viewed strictly as nervous system diseases. Can some epilepsies be in fact autoimmune-mediated? We study 'Autoimmune Epilepsy' from the following angles: 1) Identifying specific autoantibodies (Ab's) in brain and plasma of epilepsy patients, 2) Preparing such Ab's in animal models, 3) Studying the unique mechanism by which the Ab's cause damage (e.g. activating ion currents, killing neurons and impairing EEG), 4) Designing novel diagnostic and therapeutic tools for 'Autoimmune Epilepsy'.

Some of our discoveries in recent years show that: 1. Distinct subpopulations of epilepsy patients harbor elevated levels of Ab's to either the GluR3B peptide of AMPA receptors, or glutamate/NMDAR2A receptor or dsDNA, 2. Anti-GluR3 Ab's and anti-dsDNA Ab's are present on both sides of the blood-brain barrier, 3. Anti-GluR3 Ab's can activate homomeric and heteromeric GluR3 and elicit ion currents, acting alike glutamate agonists and can kill neurons. 4. The level of anti-GluR3B Ab's in the CSF drops drastically after hemispherotomy in correlation with seizure arrest and marked neurological improvement. 5. Anti-GluR3 Ab's bind GluR3 expressed on human T-cells. Taken together, our findings call for a revolutionary change in diagnostic and theraputic strategies is epilepsy, which at present completely ignore autoimmune components.



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