Animated 3D model of a novel anti-cancer drug guides experimental testing

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Background

Type-A GABA (GABA-A) receptors are chloride ion channels, which function as the major inhibitory receptors in the adult human brain. They regulate memory, cognition, sleep, and anxiety via an inhibitory or calming effect. GABA-A receptors are also present in various cancer cell types and function to move chloride ions out of the cell when activated, the opposite direction to what occurs in adult neurons (**Figure 1**). This movement of chloride ions serves to depolarize the cancer cell and trigger effects that impair cancer cell viability.

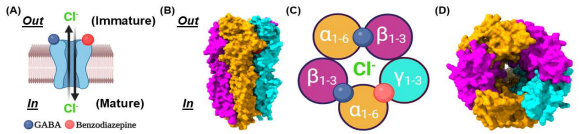

Figure 1. GABA-A receptors. (A) GABA-A receptors are chloride ion channels. In the mature neuron, they move chloride ions into the cell, while in developing or immature neurons they move chloride anions out. The natural agonist of GABA-A receptors is GABA (blue sphere). When benzodiazepines (red sphere) bind to the receptor, they serve to enhance the effect of GABA, and thus, chloride ion movement. (B) Various structures have GABA-A receptors have recently been reported. Shown is one such structure. (C) The receptors are most often hetero-pentameric assemblies composed of various subunits. Two GABA's bind to the receptor and one benzodiazepine. (D) The five subunits form a channel through which chloride ions move.

Sengupta and colleagues discovered that a novel group of drugs, members of the benzodiazepine class of compounds, take advantage of this difference in chloride ion directionality.[1,2] This group of drugs allosterically bind to GABA-A receptors in cancer cells and significantly increase the flow of chloride ions out of the cell. This also causes a flow of chloride ions out of the mitochondria, which results in its depolarization. This triggers a cascade of events, including interaction between a GABA-A receptor associated protein called GABARAP and a mitochondrial surface protein called Nix.[3] We hypothesize that these molecular interactions nucleate formation of an autophagosome and a phenomenon called autophagy or 'self-eating'.

Significance

Current standard of care treatments for primary and metastatic tumors are known to increase the risk of thrombocytopenia and febrile neutropenia and result in significant cognitive impairment. Novel therapeutic strategies to reduce treatment side effects and improve patient quality of life are needed. Sengupta and colleagues are exploring use of the novel class of drugs that activate the GABA-A receptor to potentiate standard of care and reduce its toxic side-effects.

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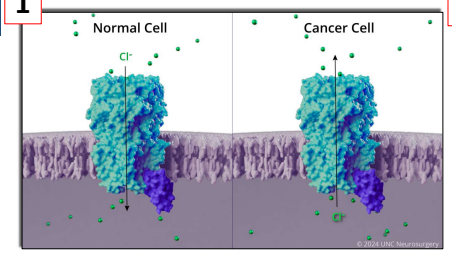

The direction of chloride ions through GABA-A receptors in normal cells is inward (left), while outward in cancers (right). This difference in ion direction is a potential therapeutic vulnerability.

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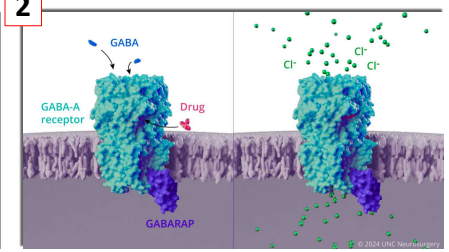

Drug (red) in the presence of the receptors agonist GABA (blue), enhances chloride ion flow out of the cancer cell (right). We are working to employ this drug as an anti-cancer therapeutic.

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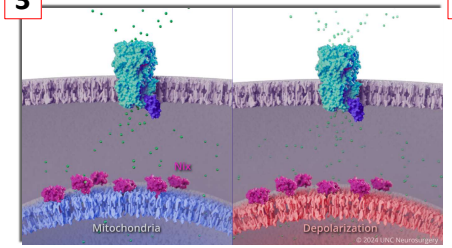

Increased flow of chloride ions out of the cell also moves chloride ions from the mitochondria, which leads to its depolarization (right). This triggers self-dimerization of mitochondrial surface protein Nix and GABA-A receptor associated protein GABARAP.

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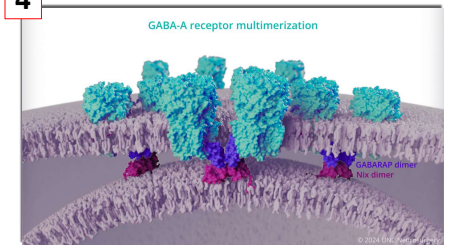

Dimers of Nix and GABARAP complex with one another. This action serves to nucleate the assembly of an autophagosome.

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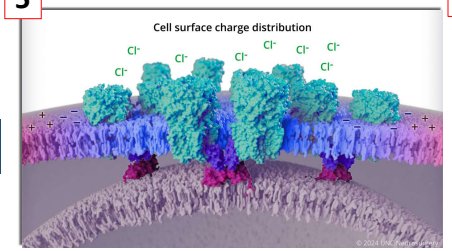

Clustering of GABA-A receptors on the surface of the cell further enhances depolarization by creating a significant surface charge distribution or polarization. Multimerization combined with the intense depolarization, promotes formation of the autophagosome.

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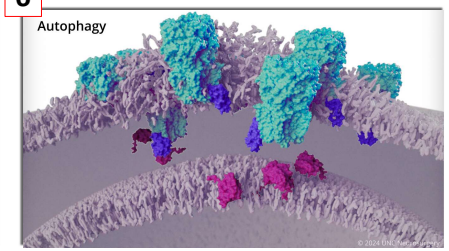

We hypothesize that autophagosome formation synergizes with standard of care treatments such as radiation and chemotherapy. In this way, our novel therapeutic potentiates these treatments.

Next Steps

This summer, I will be conducting research to test the hypothetical model presented and advance clinical applications of the novel drugs that activate the GABA-A receptors in cancer cells. Specifically, I intend to focus on treatment of medulloblastoma, a type of pediatric brain cancer located in the cerebellum (**Figure 2**). This cancer is commonly classified into four subgroups based on molecular characteristics: SHH, WNT, Group 3, and Group 4. Group 3 is of particular interest due to its significant enhanced expression of a targetable subunit of the GABA-A receptor (the GABRA5 gene), and poor clinical outcomes.[4]

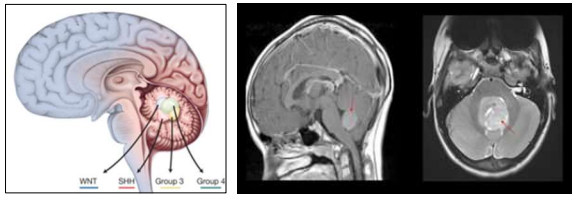

Figure 2. Medulloblastoma. (Left) Medulloblastomas occur in the cerebellum. There are four subtypes of medulloblastoma. (Right) Shown is magnetic resonance imagining of the brain of a Group 3 medulloblastoma patient.

Reference

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Acknowledgements

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