Treatment of Melanoma Brain Metastasis by Inhibition of Amyloid Precursor Protein Cleavage

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Technology

Dr. Hernando-Monge's group at NYU have discovered that Amyloid precursor protein (APP) is necessary for melanoma brain metastases to survive. APP is processed in the brain by a group of secretases to yield several products, including the Alzheimer's disease-associated protein Aβ. The investigators found a subset of proteins that were enriched in cell samples from melanoma patients with brain metastases, compared to extracranial metastasis. APP is required for melanomas to metastasize to the brain, but not to other organs, as was shown using gene silencing experiments. Moreover, brain metastases were dramatically reduced even when APP was silenced after tumors were already present. The same metastatic inhibition was achieved by blocking APP's cleavage products with an anti-Aβ antibody and with beta-secretase inhibitors.

Background

Melanomas are one of the most common cancers in the US (~100,000 new cases per year and incidence rising in the last thirty years) and the deadliest form of skin cancer. About half of patients with metastatic melanoma respond to immunotherapy, while the other half is resistant or develops severe adverse reactions to immunotherapy. Melanomas can metastasize to different organs, including the brain. Traditionally, these advanced patients are treated with immunotherapy, and in the case of brain metastases, whole brain radiotherapy and gamma-knife surgery are commonly used. However, patients with melanoma brain metastases do not respond well to these therapies and remain in need of better treatments.

Applications

- **Treatment of melanoma that has metastasized to the brain** by either blocking APP, its products, or the enzymes catalyzing its cleavage into smaller products. This can be done via monoclonal antibodies, biologics, or small molecules that bind to different targets in the APP pathway.
- **Treatment of melanoma patients prior to metastasis.** This will improve patients' prognosis as many die as a result of the secondary brain tumors.

Advantages

- **One of only a handful ways to treat melanoma brain metastasis.** Traditional cancer therapy has multiple disadvantages, such as severe side effects and resistance developed over time that limits the patient pool that responds well to therapy.
- **Highly-specific and only affects brain tumors**, suggesting it is likely to have less side effects in the clinic.
- The Aβ protein has been extensively studied in the field of Alzheimer's disease research and multiple small molecules and antibodies have been developed or are currently in clinical trials (e.g., Aducanumab [Biogen], Solanezumab [Eli-Lilly]). **The process of drug discovery will be quicker and more efficient** as some of these drugs have been screened for binding, safety, and efficacy.

Intellectual Property

US patent pending

References

1. Eva Hernando, et al.(May 2, 2022) , https://aacrjournals.org/cancerdiscovery/article/doi/10.1158/2159-8290.CD-21-1006/694183/Melanoma-Secreted-Amyloid-Beta-Suppresses