Genetic factors influencing response to immunotherapy and prognosis in patients with melanoma brain metastases

Popular Science Summary

Malignant melanoma is one of the most aggressive forms of skin cancer. While it accounts for only a small percentage of skin cancer cases, it is responsible for the vast majority of skin cancer-related deaths. A particularly dangerous and challenging stage of the disease is when the cancer spreads to the brain — a condition that affects around 50% of patients with advanced melanoma. Although immunotherapy, which boosts the patient's immune system to fight cancer, has revolutionized treatment, a significant number of patients still fail to respond or develop resistance during therapy. The reasons behind this lack of response remain largely unknown, and we currently lack reliable biomarkers to predict which patients will benefit from immunotherapy.

The goal of this project is to explore the genetic mechanisms behind treatment resistance in patients with melanoma brain metastases treated with the combination of nivolumab and ipilimumab — a regimen currently considered standard of care. To do this, we will perform whole-exome sequencing (WES), a cutting-edge technique that allows us to examine all the protein-coding regions of DNA — where the most medically relevant mutations are likely to be found. By identifying patterns of mutations that correlate with poor treatment response, we hope to better understand why some tumors evade the immune system despite therapy.

Importantly, this study will be conducted on patients already participating in a related research project (IMGEMI-COMBO), which focuses on analyzing gene expression, DNA methylation, and the tumor microenvironment using modern molecular techniques. By integrating the findings from WES with these other layers of data, we aim to build a comprehensive, multidimensional view of each tumor — uncovering how genetic mutations, immune activity, and other biological factors interact to influence treatment outcomes.

Ultimately, our aim is to discover new biomarkers — molecular or genetic signatures — that will help clinicians tailor treatment strategies more precisely to individual patients. This could not only improve survival rates in this very high-risk group but also reduce unnecessary exposure to ineffective treatments. In addition, the insights gained from this study may help identify new therapeutic targets for overcoming resistance, potentially leading to the development of better treatments in the future. The methodology we establish could also serve as a model for similar studies in other hard-to-treat cancers.