A new mouse model to study the biology of depression in cancer

Patients with advanced cancers often experience depression, which can significantly reduce their quality of life and increase mortality. Currently, the lack of a valid and useful animal model is the greatest obstacle for studying the basic biology of cancer-induced depression. The development of an animal model is vital to the effort to discover new treatments to specifically target depression caused by cancer.

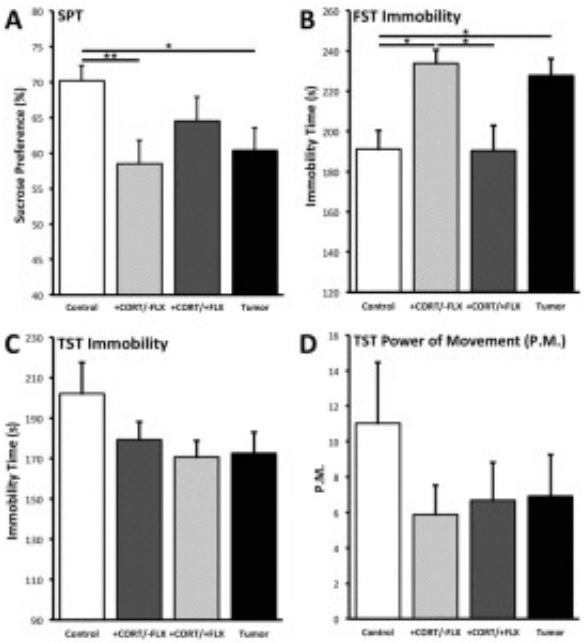

Figure 1.

To create a valid mouse model, several criteria must be met. First, we compare our proposed cancer model against an already established non-cancer depression model (positive control), and show that the depressive state in this model is reversible by a standard antidepressant. Then, we show that our proposed cancer model undergoes behavioral and neurological changes that are similar to this positive control. We used chronic administration of corticosterone (CORT), a stress hormone, to establish the positive control model. To reverse behavioral and neurological changes induced in this model, we used the popular antidepressant fluoxetine (FLX). To establish our cancer model, we injected mice with breast cancer cells beneath the skin and allowed tumors to develop.

Several behavioral tests exist to test aspects of depressive behaviors in mice. For our study, we

chose 3 tests: the sucrose preference test (SPT), the tail suspension test (TST), and the forced swim test (FST). The SPT was developed to assess anhedonia, a core depression symptom characterized by the loss of ability to experience pleasure. In this test, mice are exposed to normal water and sugar water. Anhedonic behavior is illustrated by reduced preference for the sugar water, where 50% consumption of sugar water signifies no preference at all. In the TST, mice are suspended by their tails for 5 minutes and the time spent immobile, as well as the energy expended during this time (power of movement), is measured. Similarly, in the FST, mice are placed in a container with water and the time spent immobile is measured. In both tests, the lack of struggling to escape stressful situations (immobility and/or decreased power of movement) is indicative of despair, which is a depressive behavior. Together, these two tests are the gold standards for testing new antidepressants in animal studies. Beyond the behavioral tests, we also investigated structural changes induced by these models in the medial prefrontal cortex (mPFC), a brain region known to be impacted by depression. To do this, we stained neurons in this region and examined their branching. Neurons are specialized brain cells with long branching extensions called dendrites. These dendrites form connections between neurons, and allow for the communication between cells. In depression, dendrites in the mPFC are known to exhibit reduced branching.

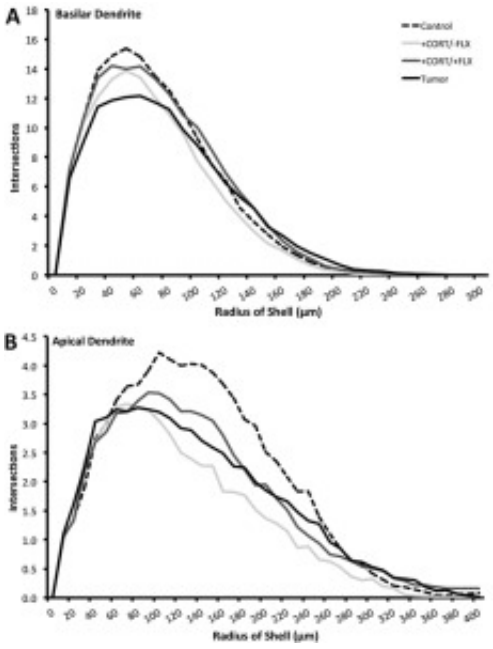

Figure 2.

In our study, we have shown that CORT causes decreased sucrose preference on the SPT, decreased power of movement on the TST, and increased immobility on the FST (Fig. 1). These behavioral changes were predominantly reversed by FLX. We also showed that tumor mice

developed very similar behavioral changes as those induced by CORT. In addition, CORT mice showed decreased branching of mPFC dendrites at both ends of the neuron (apical and basilar), which was partially reversed by FLX (Fig. 2). Similarly, tumor mice showed decreased apical and basilar dendritic branching. Therefore, we were able to validate our tumor model as a cancer-induced depression model by illustrating behaviors and neurological changes that are associated with a depressive state.

This study represents the first efforts to study the biological basis of cancer-induced depression. The model developed here will allow us to further investigate the molecular events that lead to depression in cancer, with the aim of developing new drugs tailored for this population.

Publication

Depressive-like behaviours and decreased dendritic branching in the medial prefrontal cortex of mice with tumors: A novel validated model of cancer-induced depression.
Nashed MG, Seidlitz EP, Frey BN, Singh G
Behav Brain Res. 2015 Nov 1