

DESCRIPTION FOR THE GENERAL PUBLIC

The balance between protein synthesis and degradation is crucial for cell survival. The mechanism that is responsible for degradation of proteins is known as the ubiquitin-proteasome system (UPS). The UPS is involved in the regulation of many processes including cell division, cell growth, and death. The UPS also regulates many systems responsible for cell-to-cell communication, known as cellular signaling pathways. One of the pathways influenced by the UPS is known as the Hedgehog pathway. It is essential for the normal development of humans and animals, and its abnormal activation leads to cancer. Among the components of the Hedgehog pathway, Gli proteins play an especially prominent role. They function as transcription factors, i.e. they regulate the production of other proteins. So far it has been assumed that the UPS inhibits Gli proteins by degrading them. However our preliminary results show that bortezomib, a drug that blocks the UPS, deactivates Gli proteins instead of activating them. Our results indicate that the regulation of Gli proteins by the UPS may be more complex than previously thought. The goal of our project is to attempt to explain these phenomena.

Our project is divided into three parts, each focusing on a different aspect of the problem. In the first two parts, we will study molecular mechanisms of the deactivation of Gli proteins by proteasome inhibitors. In the third part of the project we will attempt to block carcinogenesis in cancer-prone mice using the proteasome blocker. The mice that we will use have aberrantly activated Gli proteins, which, like in humans, leads to abnormally high cell division rates in the brain and to the development of a brain tumor known as medulloblastoma. Since proteasome blockers are already used in the clinic to combat other cancers, they are attractive candidates for medulloblastoma treatment.

Our results will help us better understand the molecular mechanisms of the regulation of Hedgehog pathway and activation of Gli proteins. This in turn may in the future help to design targeted therapies that will block Gli activity in cancer.