Lipid driven genetically engineered machine

Background

Lipids constitute a broad group of naturally occurring molecules including fats, waxes, sterols, fat-soluble vitamins (such as vitamins A, D, E and K), monoglycerides, diglycerides, phospholipids, etc. The main biological functions of lipids include energy storage, structural components of cell membranes, and important signaling molecules. These lipids have specific regulatory effects on gene regulation mostly through nuclear receptors.

Sponsors

1. Nuclear receptors

Nuclear hormone receptors belong to a well conserved family of proteins present in all metazoans. They may be viewed as lipid activated transcription factors. Each nuclear receptor has a conserved DNA-binding domain which contains two Zn-fingers. They can directly bind to the DNA and regulate gene expression.

2. Zn-fingers

A great deal of progress in the development of modular protein domains that recognize specific triplets of DNA sequence has been made. The domains can be fused together to create proteins that can bind to a chosen DNA sequence. Combining DNA-binding domains with effector domains yields brand new transcriptional activators or repressors, enabling us to have transcriptional control of virtually any gene of interest.

3. Apoptosis

The process of programmed cell death (PCD), is an elaborate cellular homeostasis mechanism that ensures correct development and function of multicellular organisms. Biochemical events lead to characteristic changes (morphology) and the death of cells. We would like to find a way how could we terminate our process, that why we try to induce apoptosis of the so called genetically engineered cell.

In our system we used Bax pro-apoptotic protein to induce programmed cell death which is affecting the mitochondrial pathway leading to mitochondrial outer membrane permeabilization.

Upon receiving an activating signal, a direct activator BH3-only protein such as Bid will transiently interact with Bax and Bcl-xL, causing their translocation to the outer mitochondrial membrane. Once inserted into the outer mitochondrial membrane, Bax can form homo-oligomers through BH3 domain interactions, leading to pore formation and MOMP. Bid-xL can bind to Bax via its BH3 domain and BH1l homo-oligomerization of Bax, thereby inhibiting MOMP and apoptosis.

Summary

We set up a complex system which is driven by lipids found in everyday life. We proved that several nuclear hormone receptors can be specifically activated by lipids from oil and diary products extracts (1). We also designed and tested Zn-fingers to regulate gene expression directly (2). Furthermore we found harmless way to switch off our machine by using the apoptosis (3).

We have supported 3 important mechanisms to build up a fully synthetic biological engineered cell, which is able to receive the specific signal and translocates it to the nucleus, where the tailored genetic programme could start. We also have the possibility to shutting down the program by apoptosis.