The Role of POPDC1 in the Progression of the Malignant Phenotype

Project Aim

The aim of this summer project was to collect and review the current data on Popeye domain containing proteins (POPDC), as they have been shown to play a role in the progression of the malignant phenotype. This was discussed in a review article before using molecular modelling software to develop a POPDC1 stabilising peptide.

Cancer and the Malignant Phenotype

Cancer and the formation of malignant tumours is one of the leading causes of death worldwide. The disease is characterised by various hallmarks, including rapid and uncontrolled growth (proliferation), loss of adhesion and the spread to other sites in the body (metastasis). The treatment options for cancer are based on inhibiting these processes, however, current therapis show only limited success. As the POPDC1 protein has been shown to play a role in the aforementioned processes, it presents an exciting target for developing novel anti-cancer drugs.

The Popeye Domain Containing Protein Family

POPDC1 belongs to the POPDC protein family and is present in cancer cells. It is a cell membrane-spanning protein which interacts with various downstream targets via its intracellular binding sites. A unique feature is the highly conserved POPEYE domain which can bind cyclic adenosine monophosphate (cAMP). The POPDC1 protein is often lost, destabilised or withdrawn from the membrane in cancer cells.

Figure 1 – Structure of the Popeye Domain Containing Protein 1

TREK1 VAMP3 Bnip3 LRP6 ZO-1 GEFH
aa272/273 (KK) aa242/aa246
HOOCC

(cAMP)

CAMP

aa250-aa300

PR61a

aa330-aa345

CDOH

NH3 H2N aa2 (Asn) aa30

POPEYE Domain

POPEYE Domain

(aa172-aa276)
Results

What are Cancer Stem Cells (CSC)?
CSCs are a particularly difficult aspect of cancer to treat. They use many of the signalling pathways altered by POPDC1 so determining the protein’s presence in CSCs may lead to a novel treatment to target these cells.

Figure 2 - Regulatory Roles of POPDC1 in Cancer

POPDC1 is involved in regulating numerous cell signalling pathways that lead to maintaining cell adhesion and inhibiting proliferation and metastasis. A loss of POPDC1 due to membrane withdrawal, destabilisation and under-expression, shown to be very common to cancer cells, results in decreased regulation of these pathways, allowing the progression of the disease.

Hypothesis

If POPDC1 loss in cancer cells were inhibited, the protein could continue to regulate the processes of cell adhesion, proliferation and metastasis, thereby reducing the progression and spread of cancer. A novel therapeutic agent (e.g. a small molecule or peptide) designed to specifically stabilise the POPDC1 protein in the cell membrane may therefore be a unique approach for stopping or slowing the spread of cancer.
Peptide Modelling

The cAMP binding domain of POPDC1 was used as a target for the development of a short peptide that would bind this sequence. Various structural peptide options were developed using molecular modelling and docking software. The peptides generated were then analysed according to their structure and binding affinity.

**Next Steps**

- Establish the presence of POPDC1 in cancer stem cells
- Refine and continue to analyse synthetic peptide options
- Develop synthetic peptide for further *in vitro* studying
- Develop computer molecular modelling prowess to use for educational purposes at the university