

Tumour development in Dundee

One Protein, Many Functions

Mutations in the Adenomatous Polyposis Coli (APC) tumour suppressor gene constitute an early key step in the development of colon cancer. Inke Näthke and her team are revealing what exactly goes awry without functional APC protein.

Colorectal cancer is the third most common form of all cancers and arises from small polyps which develop in the lower intestine. Although these polyps are initially benign, they can develop into cancerous growths which, if left untreated, can be lethal. Importantly, most colorectal cancers carry mutations in the Adenomatous Polyposis Coli (APC) tumour suppressor gene and these mutations occur early during tumorigenesis. The APC protein is important in many processes that govern gut tissue, from beta-catenin regulation, to regulation of the cytoskeleton.

No more binding to microtubules

This is where Inke Näthke and her team enter the picture; her group in Dundee are investigating the role of APC in this disease. Specifically, she focuses on the fact that typical cancer-related truncation mutants of APC lack binding sites for microtubules, an important element of the cytoskeleton of cells. The mutations of the APC protein in turn correlate with the disappearance of cell protrusions as well as a decrease in cell migration in these cells (*Mol Biol Cell.* 2007; 18(3):910-8). Thus these changes can be attributed to the inability of the mutant APC protein to bind to microtubules. Such weaknesses in APC-deficient cells may provide an opportunity for therapeutic intervention in the form of microtubule poisons for colorectal cancer treatment.



Inke Näthke:
No more problems with real Dundonian today.

Between architecture and differentiation

In addition, APC also binds to beta-catenin and regulates its intracellular concentration. Beta-catenin is an important mediator of cell adhesion and plays a role in regulating the activity of specific transcription factors. APC therefore interacts directly and indirectly with cytoskeletal proteins such as microtubules and regulates their stability, but also with beta-catenin that is involved in cell signalling. This multi-functional nature places APC at the interface between regulation of cellular architecture and differentiation programmes. In short, this may explain the high penetrance of APC mutations, particularly in the intestinal tract;

APC mutations constitute an extremely early stage of inherited as well as sporadic colon cancer. In addition, patients with somatic deletions in one of the APC alleles not only develop colorectal cancer but also have an increased risk for developing brain tumours and other epithelial abnormalities.

Germany, California, Scotland

Another line of research being investigated by the Näthke laboratory is chromosomal instability in tumour cells which can result from mutations in the APC gene. In short, Inke and her team have shown that loss of APC induces chromosomal instability as a result of mitotic and apoptotic defects, creating a deadly synergistic combination in early tumorigenesis (*J Cell Biol.* 2007; 176(2):183-95). Inke's long-term goal is to understand how cellular adhesion, migration and cell division are regulated in concert during development and differentiation and how changes in these processes contribute to tumour formation.

Inke's success story arose from a gap year she decided to take after completing high school. She packed her bags and left Hamburg for a year off to work for a family in sunny California. Realising that the more open, interactive approach of the American University system was something that she would not find back home in her native Germany, Inke stayed on to carry out her degree at San Jose State University, before undertaking a PhD on clathrin assembly with Frances Brodsky at the University of California, San Francisco. From there she took up a post-doc position at Stanford with James Nelson. Inke was eventually persuaded to return to European shores thanks to a chance meeting at a Gordon Conference with Birgit Lane, Director of the Cell Structure Research Group in Dundee, who informed her of the opportunities in Dundee. Inke arrived in 1998 when the £13.5 million Wellcome Trust Biocentre had just been completed. She seems more than happy with her choice; Dundee is in a beautiful environment, work is a mere five minutes away, the children

One fine day in the lab ..

*The newly discovered "violent criminal" gene was
successfully used to create a transgenic mouse...*