

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 Nätke 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 Nätke 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.

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 Nätke 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

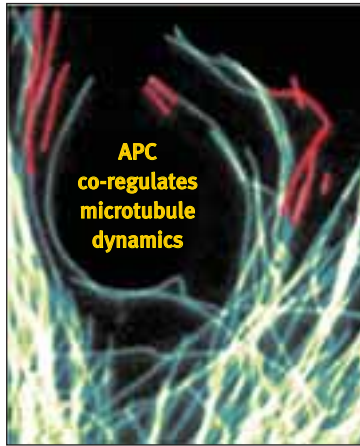


Inke Nätke:
No more
problems
with real
Dundonian
today.

are able to travel safely around the city (something that was impossible in San Francisco), and the joys of grocery shopping can be kept to a minimum. The only problem aside from the brisk Scottish weather is understanding the local Scots' broad Dundonian accent. "At first, when speaking to a real Dundonian, I was lucky to understand 80%. However, I'm improving and both my kids are good with languages so they can translate" Inke's time in Dundee has been fruitful; she is currently a Cancer Research UK Senior Fellow and Reader.

Working with clinicians

Scotland has one of the highest rates of colorectal cancer in the world, and Inke is able to collaborate with a local hospital where a comprehensive colorectal screening program is ongoing, that can provide her with important tissue samples. Working directly with the clinic's gastroenterologists, surgeons, oncologists and pathologists has helped her understand clinical aspects of the disease. "I'm learning a lot. After having seen the clinic, I come away thinking about other issues with the disease, and what is required to improve the lives of the patients. It has also taught



me how important it is to link what we learn in the experimental systems in the lab to what happens in real tissue". As recognition of her research in the field, in 2004 Inke received the prestigious ASCB Women in Cell Biology Junior Award. This is particularly meaningful as it comes from female scientists. "We had to learn quickly that if we wanted to do the things that interested us then we couldn't worry about what other people thought. That's why the award meant a lot, because it said 'you've done the right thing'".

JODY MASON

One fine day in the lab...

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



Lab Times

Founded 2006. Issue 3, 2007

Lab Times is published bimonthly

ISSN: 1864-2381

Publisher:

LJ-Verlag Herfort und Sailer

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Printed at:

Dinner Druck GmbH, Schlehenweg 6, 77963 Schwanau, Germany

Cover Artwork: Kai Herfort

Web: www.lab-times.org

Webmaster: Carsten Rees

Tel.: +49 (0)761-29 21 400; E-mail: webmaster@lab-times.org

Prices & Subscription rates:

- price per issue: €3,50

- research institutes/units: free of charge

- annual subscriptions for companies and personal subscribers: €20,-

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