

Cryptic clues drive new theory of bowel cancer development

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Dr Chin Wee Tan, Professor Tony Burgess (L-R) and colleagues from the institute have overturned the existing theory underpinning bowel cancer development.

Melbourne researchers have challenged conventional thinking on how the bowel lining develops and, in the process, suggested a new mechanism for how bowel cancer starts.

The researchers produced evidence that [stem cells](#) are responsible for maintaining and regenerating the 'crypts' that are a feature of the [bowel](#) lining, and believe these stem cells are involved in bowel cancer development, a controversial finding as scientists are still divided on the stem cells' existence.

Using 3D imaging technologies, Dr Chin Wee Tan and Professor Tony Burgess from the Structural Biology division at the Walter and Eliza Hall Institute showed for the first time the bowel generates new intestinal crypts by a process called 'budding'. The finding overturns the existing theory of how intestinal crypts form, with significant implications for our understanding of bowel cancer development.

Intestinal 'crypts' are pocket-like wells in the bowel wall that produce mucous and absorb nutrients and water. Each day, 300 cells in each crypt die and are replaced. Until now, it was believed new crypts were produced only when existing crypts 'split in half symmetrically' during early development and only regenerated in adults after significant injury.

However Dr Tan said his images showed that wasn't the case. "Using advanced 3D imaging technologies, we generated a complete view of many bowel crypts and their production at many different stages of life," Dr Tan said. "We showed new crypts continue to be produced at a low but detectable rate in adults, not only during early growth, but as a normal part of bowel maintenance."

Dr Tan said the team's findings also challenged the accepted belief on how new crypts were generated. "Our images clearly showed new crypts start from asymmetrical 'buds' that develop at the bottom of the crypt, not by each crypt splitting down the middle."

Dr Tan said the research also uncovered a likely link between crypt 'budding' and bowel cancer. "We showed that as part of normal intestinal development only one bud at a time is generated by each regenerating crypt," he said. "In precancerous and cancerous bowel tumours, we see a lot of out-of-control budding, and many buds associated with a single crypt, suggesting the genes that exert control over the budding process may have been 'lost', initiating bowel cancer development."

Bowel cancer is a leading cause of cancer-related death in the developed world. Professor Burgess said the research findings suggested although 'crypt-generating' stem cells were usually 'quiet' in a healthy bowel, they were likely to be the initiators of bowel cancer.

The critical change that led the stem cells to initiate out-of-control budding was likely related to the APC (adenomatous polyposis coli) gene, Professor Burgess said. "Eighty-five per cent of all bowel cancers have lost APC function, and all have excessive crypt budding," he said. "APC is essential for controlling crypt production and maintaining adhesion between bowel stem cells. Losing APC disturbs control of bowel stem cell location and production, causing 'chaotic' growth of crypt buds and leading directly to precancerous and cancerous growths."

Professor Burgess said the research, combined with recent studies from institute researchers Dr Michael Buchert and Associate Professor Matthias Ernst, provided strong evidence that crypt-generating stem cells were responsible for driving bowel cancer growth.

"It is essential to know whether these stem cells are driving or maintaining cancer development, as they behave very differently to other bowel stem cells," Professor Burgess said. "To target [bowel cancer](#) effectively, we need to think differently about how to kill stem cells that have lost the APC gene."

More information: Tan CW, Hirokawa Y, Gardiner BS, Smith DW, Burgess AW (2013) "Colon Cryptogenesis: Asymmetric Budding." *PLoS ONE* 8(10): e78519. [DOI: 10.1371/journal.pone.0078519](https://doi.org/10.1371/journal.pone.0078519)

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