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Understanding cell segregation mechanisms that help prevent cancer spread

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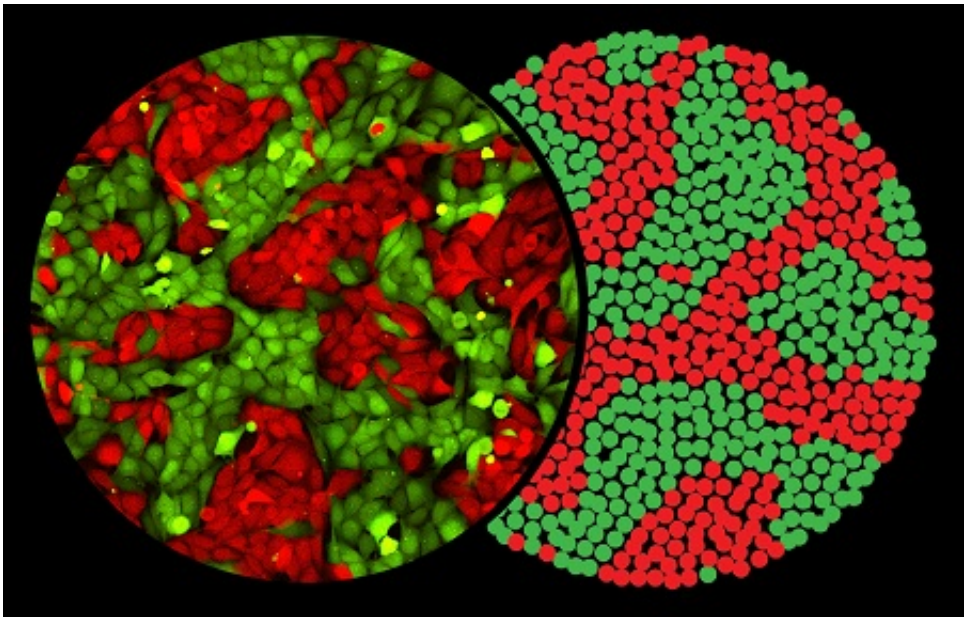

Researchers used cell imaging (left) combined with computer simulations (right) to work out how ephrins and Eph receptors keep cells in the right places. Credit: David Wilkinson

Scientists have uncovered how cells are kept in the right place as the body develops, which may shed light on what causes invasive cancer cells to migrate.

In order for organs to develop properly, cells from different tissues need to be separated by sharp borders that persist throughout our lifetime. The

mechanisms that keep cells in the right place are lost in cancer cells, allowing them to invade other cell populations and spread to different tissues.

Researchers at the Francis Crick Institute have worked out how major players in border formation between tissues—cell-surface proteins called ephrins and their Eph receptors—keep cells in the right places. The findings are published in The *Journal of the Royal Society Interface*.

In many tissues, ephrins are present in one cell population and Eph receptors in the other. When these cells come into contact, ephrins bind to their receptors, triggering signalling inside both cells that stops them from mixing. However, it was not previously known whether this was because cells preferentially stick to 'like' cells of the same type, if they repelled other 'non-like' cells, or both.

To investigate this problem, the team labelled ephrin-expressing and receptor-expressing cells with different fluorescent colours, mixed them together, and observed their interactions under a microscope as the two populations separated out.

The team used their measurements to develop a computer model of the cell interactions to help understand how they become organised.

"We found that when cells of different types contacted each other, they rebounded in opposite directions," says co-author Anaïs Khuong, Postdoctoral Training Fellow at the Francis Crick Institute. "Our simulations suggest that this repulsion is the main force separating the cell types to form sharp borders."

The team also found that when they reduced the expression of a molecule called N-cadherin that keeps 'like' cells together, the different cell types did not separate as normal. Instead, 'like' cells repelled each

other and broke into small clusters that mixed with 'non-like' cells. These findings were replicated in the computer simulations and suggest that under normal circumstances, N-cadherin suppresses repulsion between 'like' cells. This suppression is vital for 'like' cells to stick together, and to prevent them from invading 'non-like' cells enabling a sharp border to form between different cell populations.

Co-senior author David Wilkinson, Group Leader of the Neural Development Lab at the Francis Crick Institute, says: "This collaborative research between mathematical biology and developmental biology has given us new insights into how ephrins and their receptors work to keep cells in the right places, and the critical role of N-cadherin to keep like-cells together. Understanding how this signalling works will help us to figure out what might be going wrong in cancer cells to allow them to cross borders and spread through the body. Scientists are looking at potential therapeutic effects of targeting ephrin-signalling in tumours."

Co-senior author Willie Taylor, Group Leader of the Computational Cell and Molecular Biology Lab at the Francis Crick Institute, says "The collaborative ethos of the Institute brought about this project, when we realised that simulations that I had developed for interactions of molecules could be adapted to model cell interactions. The environment at the Crick is enhancing such collaboration between labs."

The paper 'Cell segregation and border sharpening by Eph receptor: ephrin-mediated heterotypic repulsion' is published in The *Journal of the Royal Society Interface*.

More information: Cell segregation and border sharpening by Eph receptor–ephrin-mediated heterotypic repulsion. *Journal of the Royal Society Interface*. DOI: 10.1098/rsif.2017.0338

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