Zebrafish provide new hope for cancer treatment

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The imaging of tumour growth in zebrafish has revealed for the first time how newly formed cancer cells have the capacity to co-opt the immune system into spreading the disease, leading the way for investigations into potential therapies for eliminating early-stage cancer in humans. Using different coloured fluorescent tags, scientists at the University of Bristol labelled immune cells and tumour-forming cells in the translucent zebrafish in order to track their behaviour and interactions by live cell imaging. These dramatic findings, which are the result of a collaboration between academic colleagues in the UK (University of Bristol and University of Manchester) and Italy (Institute of Molecular Oncology, Milan) will publish next week in the online, open access journal *PLoS Biology*.

Tests showed that cancer cells are less likely to proliferate if white blood cells can be prevented from contacting the precursor cancer cells, suggesting that white blood cells – the immune cells – have the ability to promote disease by providing some kind of growth signal. Interestingly, the chemical compound that acts as a draw between the two sets of cells was shown here to be hydrogen peroxide – commonly used as a disinfectant or antiseptic, but also a natural by-product produced by the body's metabolic process.

Describing the work, Paul Martin, Professor of Cell Biology at the University of Bristol's Schools of Biochemistry and Physiology & Pharmacology, who supervised post-doctoral fellow Yi Feng in the research project, said: "By visualizing the earliest interactions between

cancer cells and their host environment, we have shown that even from their earliest stages tumours don't just avoid being destroyed by the immune system. Rather, they appear to court an immune response, co-opting the body's innate immune system to aid and abet their growth."

The team used a method to switch on the human oncogene, HRAS, in specific pigment cells (melanocytes) in the skin of early stage zebrafish embryos. Studies were carried out using zebrafish because they conserve many of the molecular and cellular components of tumour formation seen in mammals and are almost translucent, making it easy to see the cells as they move around and grow. Researchers monitored the first hours and days of development and as the embryo grew, some of the cells were transformed, ie, made cancerous by HRAS. Those transformed cells were found to actively attract the innate immune cells. The researchers got the same results, after inserting HRAS into different, mucous-secreting cells, and again when experimenting with a different oncogene, SRC. They discovered that the tumour cells produced hydrogen peroxide and that immune cells were drawn up the hydrogen peroxide gradient towards the cancer.

The researchers' movies show that the immune cells appear to engulf cancerous cells in a bid to destroy them. However, other cells formed cytoplasmic tethers linking them to cancerous cells and in some cases the cancerous cells appeared to drag the immune cells back when they started to leave the region. In order to see whether the tumour was avoiding destruction or actually co-opting the immune cells, the researchers blocked the immune response in three different ways: they prevented the development of immune cells for the first three days of the zebrafish embryos' life, and separately, they used two different strategies to limit hydrogen peroxide production. In each case, immune cells failed to migrate to the cancer site. And each time, when the immune response was blocked, fewer cancer cells formed.

Professor Martin added: "Yi's movies in Zebrafish larvae give us the first insight into how immune cells sense and then attempt to deal with the earliest stages of cancer. Now we can look closer to discover why it is that immune cells seem to aid growth of these young cancer cells and figure out ways for guiding immune cells how better to search and destroy."

More information: Feng Y, Santoriello C, Mione M, Hurlstone A, Martin P (2010) Live Imaging of Innate Immune Cell Sensing of Transformed Cells in Zebrafish Larvae: Parallels between Tumor Initiation and Wound Inflammation. *PLoS Biol* 8(12): e1000562. doi:10.1371/journal.pbio.1000562

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