ABOUT CANCER, GENES AND CIRCULATING TUMOUR CELLS

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What is cancer and how does a normal healthy cell become cancerous?

Most cells in our body are continuously dividing, different types of cells at different rates. Each cell contains DNA, a long molecule that holds the genetic code necessary for the cell to function both as a single unit and as part of an entire organism. Before a cell divides, it has complex mechanisms in place which check that all the DNA has been duplicated correctly. A mistake in the duplication of the DNA means that a gene has 'mutated' and no longer contains the correct code. These mutations are normal and happen all the time in healthy cells. A healthy cell will recognise these mistakes and activate genes which make DNA repair 'kits.' These repair kits will literally go to the spot on the DNA that is mutated and correct the mistake. The cell then checks that the damage has been repaired correctly, and then goes on to divide into two daughter cells.

Genes are segments of DNA that 'spell out' the instructions for a cellular function. When there has been damage (or mutation) to a gene that regulates the cell cycle, we call this cancer.

These cell-cycle-control genes can be categorised as follows: genes that check that DNA has been copied correctly; genes that make DNA repair kits; genes that control growth promotion; genes that inhibit excess growth; genes that stimulate natural cell death, and genes that limit the number of times a cell can divide during it's lifetime.

If the gene that is responsible for checking that the DNA has been duplicated correctly is damaged, then the mechanism for checking will be faulty and will not pick up that there is damage in the DNA strand. As a result, the cell will go on to divide, thereby passing on these defunct genes to their daughter cells.

Subsequent generations of cells which inherit this damage are unable to regulate their cycle from outset. They continue to accumulate mutations and divide irrespective of this damage to the DNA. In a nutshell, cancer is a cluster of dysfunctional cells that are dividing to form a mass. This is the tumour which will eventually compress surrounding structures and deplete the surrounding tissue of nutrients, upsetting the balance of normally functioning organs.

What is the difference between benign and malignant cancer?

A primary cancer is a tumourous mass of cells that have 'inherited' defunct DNA and are dividing uncontrollably. It is not that they are dividing faster; it is simply that the mass has a higher proportion than it should of cells that are actively dividing. The major difference between a benign tumour and a malignant tumour is that a benign tumour will stop growing if the growth stimulus is removed. The cells in a malignant tumour will keep dividing and the tumour growing. The cells of a benign tumour will very closely resemble healthy cells, whereas malignant tumour cells will have accumulated a greater number of mutations and will become totally different in look and in function to the surrounding cells or the cell from which it is derived.

What are metastases?

Cells in a malignant tumour will be accumulating new mutations with each life-cycle. This means

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that there will be different types of malignant cells within the one tumour. They are all organised in a way that supports tumour growth. Some will be stimulating the formation of new blood vessels so as to guarantee nutrition; some will be making growth-factor hormones to stimulate a greater rate of cell division etc.

The subpopulation of cells which detach from the primary tumour mass, migrate through the surrounding cell matrix and into the blood stream. These are the **metastasising population of tumour cells**. These cells circulate in the bloodstream and are called '**Circulating Tumour Cells',** often abbreviated to '**CTCs**'. At the point of dissemination CTCs will exit from the blood stream and settle in an organ or body part that is foreign to where it came from. The CTC will have all the information necessary for initiating and maintaining the growth of a new tumour at the new site. This information is coded in the mutations which it has accumulated over many life cycles. The information will include such things as how to attach to a new type of surrounding organ; how to stimulate the organ to release growth factors that stimulate growth of cells and new blood vessels etc.

What is DNA? What is a gene? What is a mutation?

In brief, DNA is a long molecule that stores information. DNA is located in the centre (nucleus) of every cell and contains all the instructions necessary for the organism to function. Similar to pearls on a necklace, along the DNA strand there are millions of basic structural units called nucleotides. Each nucleotide (pearl) is one of four types, 'A, T, C, or G' as determined by the amino acid they contain, i.e. nucleotide 'A' has Adenine, 'T' has Tyrosine, 'C' has Cysteine and 'G' has Guanine. These four types of nucleotides are arranged along the strand of DNA in such a way that their order spells out a code that can be 'read' and acted upon by cellular components, i.e., if you were to read a segment of DNA, it might look something like 'AATGTGCTGAAGTCTGAACT.' This very segment of DNA may be the instructions that, for example, the skin cell needs in order to make the keratin protein that functions to protect the skin from abrasion. The DNA segment, or 'set of instructions,' is called a gene.

A gene is simply a set of instructions that a cell needs in order to make something useful. Genes instruct the making of such things as collagen, pigments for hair colour, enzymes etc.

Your DNA is unique to you, and your DNA is identical across all the cells in your body.

It is the specific *function* of a cell that determines which genes will be read and which instructions carried out. Using the example of making keratin protein; skin cells are one of the only cell types that use the segment of the DNA containing the instructions that are needed to make keratin proteins. That same gene will be in the same place on all other DNA strands in the other cells of the body, but may not be unpacked or read or used. It will nevertheless be there. If a gene is read and something (e.g. keratin) is made as a result, in scientific language we say that it is '**expressed.'** Cancerous genes express specific proteins that identify the cell as cancerous.

What role do genes play in the initiation and progression of cancer?

If something is 'carcinogenic' (e.g. asbestos), it means that it has the capacity to irreparably damage the exposed cell's DNA at the site where the genes for cell-cycle-control are located. All this means is that the sequence of As, Ts, Cs and Gs in that crucial gene segment is mucked up or mutated. A mutation can be as tiny as a G-nucleotide being replaced by an A-nucleotide in the sequence, or a couple of nucleotides being cut out or accidently inserted. Conversely it could be as massive as an entire segment being translocated to a foreign spot on another part of the DNA strand. As mentioned before, these mutations are usually picked up and rectified by cell-cycle-control genes. But if the mutation is in one of these crucial control genes, then the mechanism for picking up the mistake isn't functioning. This occurs when the cell goes on to divide despite having defunct genes, and hence, when the DNA is copied prior to cell division, the copy is also wrong, thereby instigating the inheritance of dysfunctional cell-cycle-control genes.

Cancer is recognised in the laboratory by testing for the existence of proteins that are made only by

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cancerous cells. These are called 'biological markers' and are made with instructions from mutated genes.

An example of a biological marker is 'HER-2' present in the more aggressive breast cancers. Biological markers influence treatment choice. A good example of this is that of breast cancer patients whose tumour cells have the 'cerb-2' biomarker. Here oncologists may prescribe a very specific treatment (Herceptin) for these patients due the presence of this biomarker.

What are Circulating Tumour Cells (CTCs)?

From the time malignant tumours have reached a size of 1-2 mm, they release thousands of malignant cells into the circulation. Most of those die or get killed off. The more aggressive ones survive and remain in the circulation as CTCs. They have the potential to dispatch into a foreign site in the body in order to proliferate and create a 'secondary cancer,' also known as a 'metastasis.' Their ability to do this is unique to CTCs, i.e. the rest of the population of tumour cells is not able to do this.

The ability for CTCs to metastasise is made possible by the particular genetic mutations which the CTCs have accumulated and passed onto subsequent generations.

CTCs contain the genes that govern the growth of a secondary cancer. For example, there will be a gene which instructs the making of hormones which will stimulate healthy cells in the new site to make a new network of blood vessels, (needed to supply the new tumour with nutrients).

Without CTCs, a metastasis cannot occur. (Even though CTCs have yet to be defined in a medical dictionary, 'metastatic insufficiency' is officially defined as the elimination of CTCs).

CTCs are a hot topic in cancer research laboratories worldwide.

Due to their capacity to initiate secondary cancers, CTCs are becoming the target for the future tailoring of cancer treatments.

What information will the detection and analysis of CTCs give to my Oncologist and Health Practitioner?

Thus far, it has been impossible to predict how two people with the same type of cancer will respond to treatment. Through the analysis of CTCs it is possible to provide clinicians with information to help overcome this challenge. CTCs contain all the information for the establishment of a secondary cancer. Therefore, with the use of new molecular technology, it is now possible to determine the exact nature of a patient's actively metastasising cancer cell population (CTCs).

Simple detection of CTCs in the bloodstream means "micro" metastases of malignant cancer may be detected a lot earlier than they may be with conventional methods of detection (such as scans and tumour markers). A standardised measurement of the number of CTCs in the blood is recognised as a prognostic indicator. The prognosis may include risk of recurrence, further possible tumour progression, and other possible prognostic markers. Sample collection is easy via approximately 20mls of peripheral blood. This makes it possible to monitor the progression of the tumour, the success of surgery, and the success or response to treatment.

Because CTCs have different properties to the rest of the tumour cells, not only do they have the capacity to initiate another tumour, but they may have totally different biomarkers to the original cancer from which they came. Analysis of CTCs may unveil these biomarkers, some of which might indicate resistance to treatment. By isolating and testing CTCs, it is possible to predict how your cancer will respond to radio- and chemo-therapy, and natural therapies. This knowledge helps to give your oncologist and Health Practitioner a clearer understanding of the nature of your cancer which may influence decisions about designing a targeting therapy specific to the patient's individual cancer properties.

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Where can I get some more information?

- Genostics website: www.genostics.com.au
- The Cancer Council's website is http://www.cancer.org.au/aboutcancer.html
- National Cancer Institute (U.S) general info at http://www.cancer.gov/ OR
- NCI molecular diagnostics for more information about molecular (genetic) diagnostics
- The UK Macmillan Cancer Support website is at: http://www.macmillan.org.uk/Cancerinformation/Cancertypes/AtoZ.aspx
- Informative video: How DNA 'codes' for YOU: http://www.khanacademy.org/science/biology/evolution-and-natural-selection/v/dna
- Informatiove video: How cancer is the by-product of the breakdown of DNA replication http://www.khanacademy.org/science/biology/cell-division/v/cancer
- Genostics has practitioner information folders available upon request.

And please consult your medical specialist.

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