Cancer and stem cells are both topical issues. But have you heard of cancer stem cells? As Massimiliano Mazza explains, this concept may revolutionise the treatment of cancer.

Cancer: an evolving concept

*If thou examinest a man having tumours on his breast, (and) thou findest that swelling have spread over his breast (...) thou shouldst say concerning him: “One having tumours. An ailment against which I will fight.”*

This first known reference to a tumour, on an Egyptian papyrus\(^1\), is attributed to Imhotep – vizier, architect, physician and astronomer to Pharaoh Djoser, in 2500 BC.

A tumour (from Latin *tumor*, meaning swelling) is a tissue mass caused by the abnormal proliferation of cells, but it is not always associated with cancer. Tumours that are confined to a...
specific region of the body are known as benign – they may cause health problems but are not necessarily life-threatening. In contrast, a tumour that spreads within the body, invading adjacent tissues and often metastasising (spreading to tissues and organs elsewhere), is called malignant; this is cancer. Although humans have been aware of cancer for more than 4000 years, our understanding of it has only improved significantly in the past 200 years.

An important contribution to the study of cancer was made in the 19th century by German physiologist Johannes Müller and his student Rudolf Virchow. Benefitting from recent advances in microscopy, they understood that cancer is an aberration of cell behaviour, rather than being generated de novo. Virchow was the first to realise that this happens through a combination of genetic predisposition and chronic irritation, such as that caused by smoking or ultraviolet radiation. As we know today, cancer begins with a single cell that loses control over its growth as it accumulates genetic mutations – both spontaneously and as a result of environmental factors – sometimes over a period of many years.

Cancer heterogeneity and cancer stem cells

The microscopic dissection of tumours in the 19th century also revealed that the morphology of even a single tumour may be remarkably heterogeneous. A tumour always originates from a single cell, so how can its daughter cells vary so much? There are two reasons: first, as they divide, the cancer cells accumulate further mutations that make them genetically different from one another; and second, the microenvironment varies across the tumour and this influences how each cancer cell behaves.

Let us take a look at the genetics first. In certain types of skin cancer, for example, an epithelial cell accumulates mutations, often over many years, and becomes cancerous – proliferating to form a group of epithelial cancer cells. Just like a population of animals, this population of cells evolves as it accumulates further mutations. Those mutations that give a cell a competitive advantage over other cells will result in a clone of similar cells, whereas other mutations will be disadvantageous and may even kill off the cell. By the time a tumour is detected, the different clones of cells that make up the lump may have become distant relatives.

The second influence is the microenvironment of a cancer cell: the cells, structures and molecules around it. As the epithelial cancer cells proliferate and the tumour grows, it incorporates cells from the surrounding tissue, until it consists not only of cancer cells but also of many different types of non-cancerous cells. These can include supporting cells of the connective tissue, blood vessels that supply the tumour with nutrients, and immune cells that enter the tumour from the bloodstream.

This article puts forward the current theory that there are cancer stem cells in much the same way as there are other stem cells. The article could make a good basis for a general discussion of the topic of cancer, including cancer research and treatments, diagnosis and survival rates. Why are some cancers more treatable than others? Differences between bone marrow transplants, chemotherapy, immunotherapy, radiotherapy and vaccination can be researched and discussed. Why is there no vaccine for cancer? How does the vaccine for human papilloma virus work to prevent some cervical cancers (it has to be remembered that this is not a vaccine against the cancer itself)? Some cancers involve chromosomal rearrangements – this would lead on to the topic of cytogenetics. Most students have encountered someone with cancer and they will be able to engage with the topic.

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stem cells’ was chosen because, like stem cells in normal body tissues, they can either produce more cells like themselves, or differentiate to form different cell types. Scientists are still debating which of the two models (stochastic or hierarchical) best fits the experimental results, but there is mounting evidence from studies of several cancer types that a small subset of cells are responsible for tumour maintenance and initiation. If so, these are CSCs.

Cancer stem cells in cancer therapy

Currently, despite treatment with chemo- and radiotherapy, many cancers recur and metastasise to other organs – these are the circumstances of the majority of cancer patients that
die. Why is this? The reason could be CSCs. Because of their slower cell cycle, they might survive the treatment, allowing the tumour to regrow later.

Conventional chemo- and radiotherapies for cancer specifically target fast-dividing cells, because most cancer cells proliferate much faster than normal cells. The treatments are designed not to harm slowly dividing cells, such as normal stem cells and most other cells in our body. After patients with acute myeloid leukaemia are treated with these therapies, their haematopoietic (blood-forming) stem cells begin to proliferate to replenish the pool of blood cells. However, scientists have found that the CSCs that have survived start proliferating then too, regenerating the bulk of the tumour with cells even more aggressive and treatment-resistant than before.

The obvious solution, then, would be to develop therapies to specifically target CSCs. This is not easy though, because scientists are still struggling to find reliable methods to detect which cells in a tumour are the CSCs. The idea, however, is for those types of cancer where the CSC model holds true – such as brain, breast, colon, ovarian, pancreatic and prostate cancers – to combine therapeutic strategies that target the fast-dividing cells with strategies that make the slowly dividing CSCs proliferate faster, so that they can be killed off, too.

Over the next few years, scientists hope to find out whether the CSC theory is a real breakthrough for cancer treatment, or if a more accurate model of cancer is still required.

**Web reference**
w1 – For translations of the Edwin Smith papyrus in English and German, see: www.touregypt.net/edwinsmithsurgical.htm and www.medizinische-papyri.de/Papyrus-Smith

**Resources**
The University of Rochester Medical Center has produced a lesson plan for an upper secondary-school activity on cancer stem cells. See the university website (www.rochester.edu) or use the direct link: http://tinyurl.com/63jfds

Harvard scientists have recently discovered that CSCs may be generated from other cancer (non-stem) cells – so that eradicating the CSCs
Bone marrow smear of T-cell acute lymphoblastic leukaemia

Joan Massagué is an inspiring cancer researcher. For an interview with him, see:

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Massimiliano Mazza has been doing post-doctoral work in the Experimental Oncology Department at the Istituto Europeo di Oncologia (European Institute of Oncology) in Milan, Italy, since September 2007. He works on models of acute myeloid leukaemia in mice, and is particularly interested in CSCs.