

# The replenishers

*It has long been thought that cancer cells are immortal and that their ability to divide is limitless. Doubt has now been cast on this mindset, as new research findings suggest that most tumor cells have inherited this ability from their precursors, tissue stem cells. Professor Otmar D. Wiestler, Board Chairman and Chief Scientific Officer at the German Cancer Research Center (DKFZ) in Heidelberg, is therefore calling for further research into cancer stem cell biology. This could open up new treatment approaches targeted specifically at these cancer replenishers.*

We take it for granted that our body's tissues and organs will function properly all our lives. Many specialized cells in the lining of the intestine or in the blood, for example, have a lifespan of just a few days, however. All the more amazing, then, that white blood cells are still around to fight off infection even in old age or that the digestive tract is still functioning satisfactorily even after 70 years. The ability of most tissues to function all our lives is down to a special type of cells known as tissue stem cells or "adult" stem cells.

Stem cells have two defining characteristics. Firstly, they must produce all the different cell types that make up their particular tissue, a property that is known as pluripotency. Both red and white blood cells, for example, originate from blood stem cells. Secondly, they have to renew themselves so that they can replenish different tissue cells for a whole lifetime. The best studied processes are those involved in blood cell formation. Some decades ago now, the small population of blood stem cells was discovered in the bone marrow that develop progressively via a number of now well-understood stages into the various mature blood cells. Back in the 1970s, American researchers concluded from this that leukemias (blood cancers) originate not from just any old malignant blood cells but that a flaw in the programming of the blood stem cells flushes into the blood a constant stream of malignantly changed, functionally incompetent cells of the most diverse types.

Experimental proof of this hypothesis was provided in the 1990s. If the heterogeneous leukemia cells are sorted according to their surface molecule and these "single type" cell populations are transplanted individually into mice, just one small subgroup triggers the disease again in the animals. This population has the same surface marker profile as blood stem cells. Shortly afterwards, the animals with "transmitted" leukemia again display the whole spectrum of different types of cancer cells as in the original disease. In other

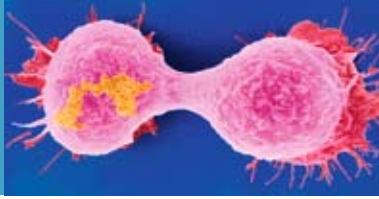
words, the transplanted tumor stem cells have the ability to differentiate.

This is an exciting concept that provides new explanations for an old observation. Pathologists have long known that cancer is not an accumulation of identical, malignant cells but that different cell populations develop within a tumor. Until now, this has been believed to be a consequence of the ever-increasing mutations in the cancer cells. It could, however, also be a case of out-of-control differentiation, similar to normal organ development but with fatal consequences.

## Degenerated tissue stem cells as the possible cause of cancer

Many key types of cancer develop in the epithelial tissues lining the cavities of all body structures: bowel, stomach, upper digestive tract, airways, milk ducts of the breast, uterus and skin. A common feature of these epithelia is that their cells have to be replenished from a stem cell population at regular intervals. This led to the assumption that these cancers might originate from malignantly changed tissue stem cells. The first proof came for breast cancer. Transmission of the breast cancer cells to animals was possible only with a single subpopulation, characterized by particular surface markers. In the case of some epithelial tumors such as prostate cancer and recently also bowel cancer, there is now evidence of the existence of cancer stem cells. More of a surprise was the discovery of cancer stem cells in tumors of the nervous system such as glioblastoma and medulloblastoma, as it had long been assumed that nerve tissue does not regenerate and therefore also does not contain tissue stem cells.

Our knowledge of the characteristic surface markers of stem cells in particular tissues is still limited. It is largely unknown whether what we currently refer to as cancer stem cells result directly from pluripotent tissue stem cells or from



Pioneering thinker: Professor Otmar D. Wiestler from the German Cancer Research Center (DKFZ) is hoping that research into cancer stem cells will create new approaches to tumor therapy.

one of the subsequent stages of cell differentiation. Furthermore, we do not yet know what their immortality means at molecular level. A few key molecules of central signal transmission pathways have already been identified, however. It emerged from this that the same regulatory mechanisms are often in action in stem cells and cancer stem cells. A great deal more research is nevertheless necessary if we are to properly understand such processes.

The concept of cancer stem cells could have dramatic repercussions as regards the treatment of cancer. Treatments of the future will have to specifically target the small group of cells that sustain the cancer. After all, only this small fraction of all tumor cells is of relevance to the cancer. New diagnostic methods will also be needed for specifically tracking down

cancer stem cells rather than counting "merely" the number of circulating tumor cells in the patient's blood. The concept of cancer stem cells is also a determining factor, however, in the development of active substances or immune therapies to inhibit specific tumor cell enzymes or receptors. In particular, we now need to investigate whether these target structures are also formed from the cancer stem cell population.

### Therapeutic approach: cut off tumors from their back-up reserves

In addition to their potential immortality, cancer stem cells have inherited a number of other undesirable properties from tissue stem cells. They are highly mobile and have an ample supply of DNA repair enzymes and membrane transporters. As a result, they can colonize tissues some distance away and are more resistant to radiotherapy (as they immediately repair damage to their genetic material) and chemotherapy drugs, which they simply remove from the cell using transport proteins. Many of the conventional therapies consequently never actually reach their intended goal. We therefore need to reconsider. Up until now, we have measured the success of a cancer therapy in terms of whether it quickly kills off as many cancer cells as possible. This usually means that the majority of the "differentiated" cancer cells are destroyed, a loss that is nevertheless immediately replenished from the pool of tumor stem cells. In contrast, a therapy targeted specifically at stem cells would initially result in no discernible regression of the tumor but would still cause it to wither with time on account of a lack of replenishment. This goal will only be achieved if we figure out what makes a life-sustaining tissue stem cell turn into a life-threatening cancer stem cell.

 [www.dkfz.de](http://www.dkfz.de)  
*The homepage of the German Cancer Research Center (DKFZ) offers comprehensive information on the most recent findings in cancer research.*