Cancer – 200 Different Diseases

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Are cancer cells in conflict with healthy cells? Is cancer inherited? What new therapies are currently being developed? We talk to Prof. Janusz A. Siedlecki, who has been studying the mechanisms of carcinogenesis for over 40 years, and has focused on molecular diagnostics for the last two decades

Academia: Robert Weinberg, writing about oncology, called cancer cells "selfish." Would you call this an accurate expression?

Janusz A. Siedlecki: *It's more of a literary metaphor. I wouldn't describe cancer cells as being enemies of healthy cells, since differences between them involve disruptions to an existing and delicate metabolic equilibrium arising from changes to the cellular genome. If a gene is damaged, the proteins formed by this damaged matrix often lose their primary properties. This affects how equilibrium systems are regulated in healthy cells, with disruptions to cellular homeostasis thereby taking place. I think it is inaccurate to describe cells as having "selfish" or "unselfish" properties. Put simply, as a result of changes to genetic material, certain processes occur leading to either cellular death or neoplasia.*

But surely such dysregulated cells are harmful to the body.

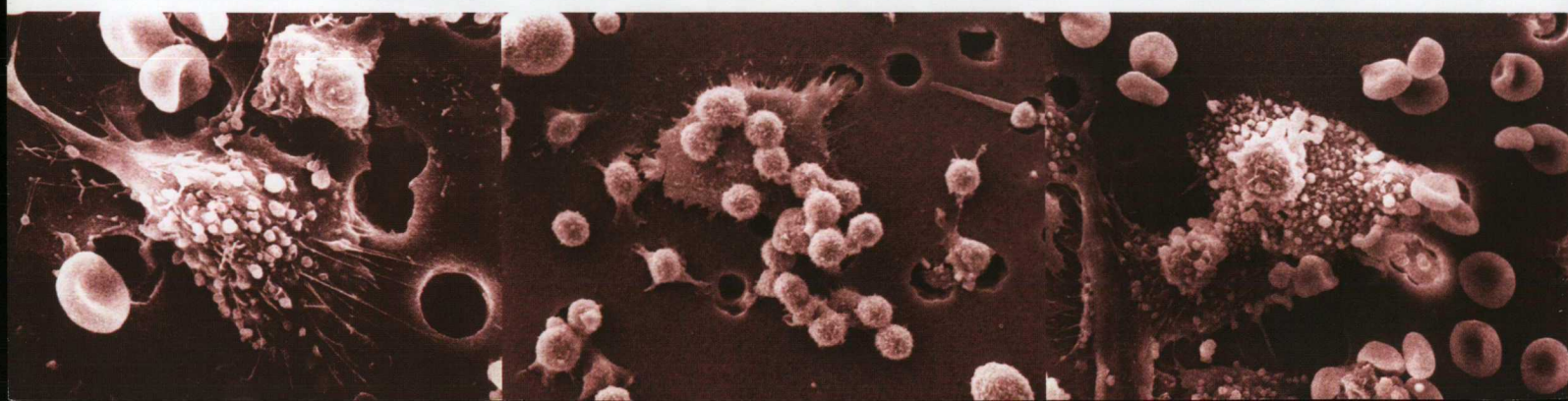
That's only our interpretation; these cells bear no ill will towards healthy cells. However, changes in their genome do give them a selective advantage. This means that they are able to take better advantage of the body's resources, and are able to proliferate far more frequently than healthy cells. Changes to the cell's genetic material usually mean that cancer cells gain a survival advantage.

What is the genetic basis of cancer? We talk about a cascade of mutations necessary for cancer cells to metastasize.

In the seventies, most scientists thought that cancer results from the progressive accumulation of somatic mutation, leading to an increased deregulation of key molecular pathways. Since then, this paradigm has undergone a gradual change. With increasing knowledge about cancer, the term "mutations" has gradually come to be replaced by "alterations"; these may occur at the chromosomal or DNA sequence level, or they can be epigenetic. And they can be irreversible. Epigenetic changes are modifications to the genetic material that do not affect the base sequences of the DNA strand. These may occur at transcription or translation levels or may affect regulatory elements, such as non-coding RNA. This means that the original mutation theory has become updated and modified to take into account the damage to genetic material, as long as it is understood that it applies to chromosomal translocation, DNA mutations, epigenetic changes, transcriptional changes, translation changes, etc.

You mentioned that some changes may be caused by environmental factors. But aren't certain predispositions to cancer hereditary?

The majority of cancers originate from somatic cells rather than gametes. Cells accumulate numerous changes throughout their lifetime.



Most damage is repaired on an ongoing basis, but some remains, slowly changing the cell's phenotype. When changes reach a critical level, then in 95% of cases, the cell becomes cancerous. In other words, the majority of cancers arise from successive changes in somatic cells. Of these, 5% are cancers with a strong genetic basis. I am deliberately not using the word "hereditary," because the term is incorrect. We can talk about heredity when we are 100% certain that an illness is the result of damage to a specific gene; with cancers, we don't have such a simple relationship. Carcinogenesis occurs as a result of numerous changes and we cannot say yet how many;, although recent research indicates that there may be fewer than was previously thought, because many of them are secondary. Cancerous changes can be divided into two types of mutations: "driver mutations," which induce phenotype changes, and accompanying "passenger mutations," which may or may not be important to the process.

So what is the risk that my own cells will undergo changes leading to cancer?

Epidemiological data indicates that the chances are approximately one in four – this means that a quarter of the population will develop cancer at some stage of their lives. But it's important to ask how many of those people go on to make a recovery, and this largely depends on where they are treated. For example, if a breast cancer patient receives treatment at our oncology center, she has an 80% chance of recovery; however, without such specialist cancer care, this drops to around 40%. This is because oncology treatment involves a combination of several different therapies. We have dedicated cancer surgeons, as well as specialist radiotherapists, chemotherapists and endocrinologists; we provide molecular diagnostics which allow us to devise complex treatment programs aiming to halt aberrant metabolic processes. Other hospitals, even in Warsaw, are unable to fully provide such a complete range of treatment. Of course we are not the only institution of this type in Poland; there are 16 other similar specialist oncology centers. New facilities are also being built, including private hospitals, but they don't always provide the full available range of treatments and technologies.

Prevention is an important topic when discussing cancer. But is it possible to detect cancer before a tumor is formed?

There is no single test for cancer, because the term actually covers around 200 different diseases. Each type involves different changes. Additionally, if we were to analyze ten cells collected from a single tumor, each one would contain thousands of different changes. Some will recur – these are the driver mutations – while the others are typical passenger mutations resulting from individual differences. Pathologists classify cancers into specific types; different types are treated differently. We are also trying to come up with a similar classification at the genetic level. So far this has been possible for a few cancers, including breast cancer. Treatment always begins after a histopathological diagnosis.

In an ideal situation, we would like to diagnose cancer before the tumor starts proliferating, but existing imaging technologies do not allow us to detect changes smaller than 2mm in diameter – the in-situ stage. The stuff of dreams would be to have a tricorder (a portable tool from the Star Trek series, used to make an instant diagnosis by scanning over the patient), but so far this is still confined to the realm of science fiction.

But it is possible to pay for a genetic analysis at a private laboratory to check for mutations that increase the likelihood of certain cancers. That's the type of analysis that led Angelina Jolie to decide on having a double mastectomy.

Although there are hereditary elements that contribute towards developing certain cancers, really powerful genetic links exist in only about 5 to 10% of cases. There are tests for detecting our predisposition to developing these types of cancers, but it's important to remember that even if such a mutation is found, it doesn't mean the disease is inevitable; it simply means that the risk of its developing is greater than average. Additionally, the risk increases with

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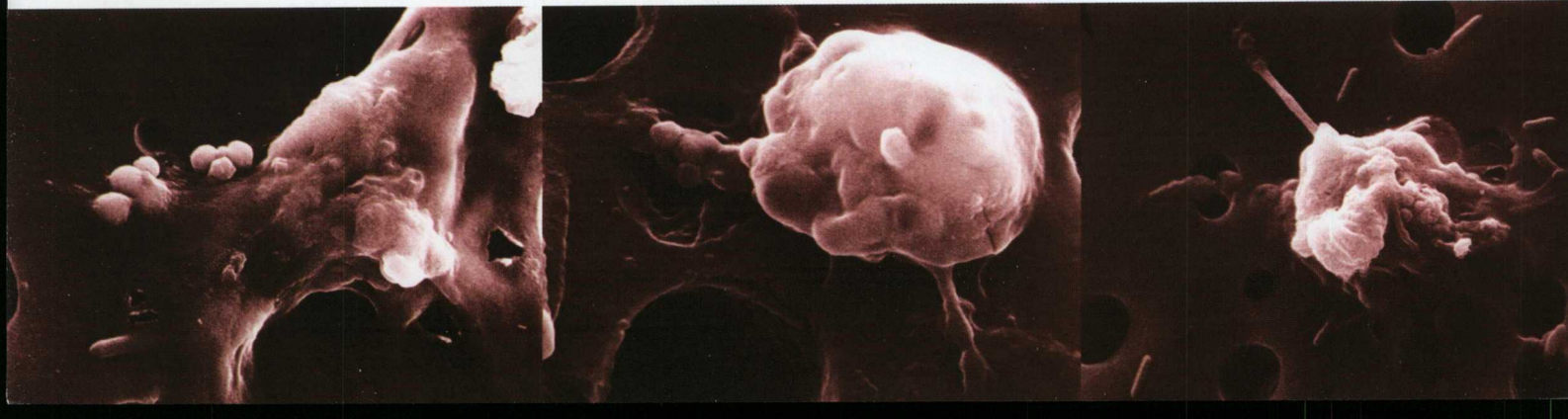


Cellular sequence of a tumor cell. A migrating cancer cell (photo 1) is surrounded by cells of the immune system (photo 2), which attack it with their secretions (photo 3); as a result, the cancer cell changes shape and loses its distinctive protrusions (photos 4 and 5). Eventually it shrinks, collapses in on itself and dies (photo 6)

age – the younger the patient, the less likely they are to develop cancer. In breast cancer, a mutation in the BRCA1 and/or BRCA2 gene is linked to a high predisposition to developing the disease. Jolie made her decisions on the basis of test results showing that she carries this mutation. However, while surgery has reduced the likelihood of her developing cancer, it has not been fully eliminated.

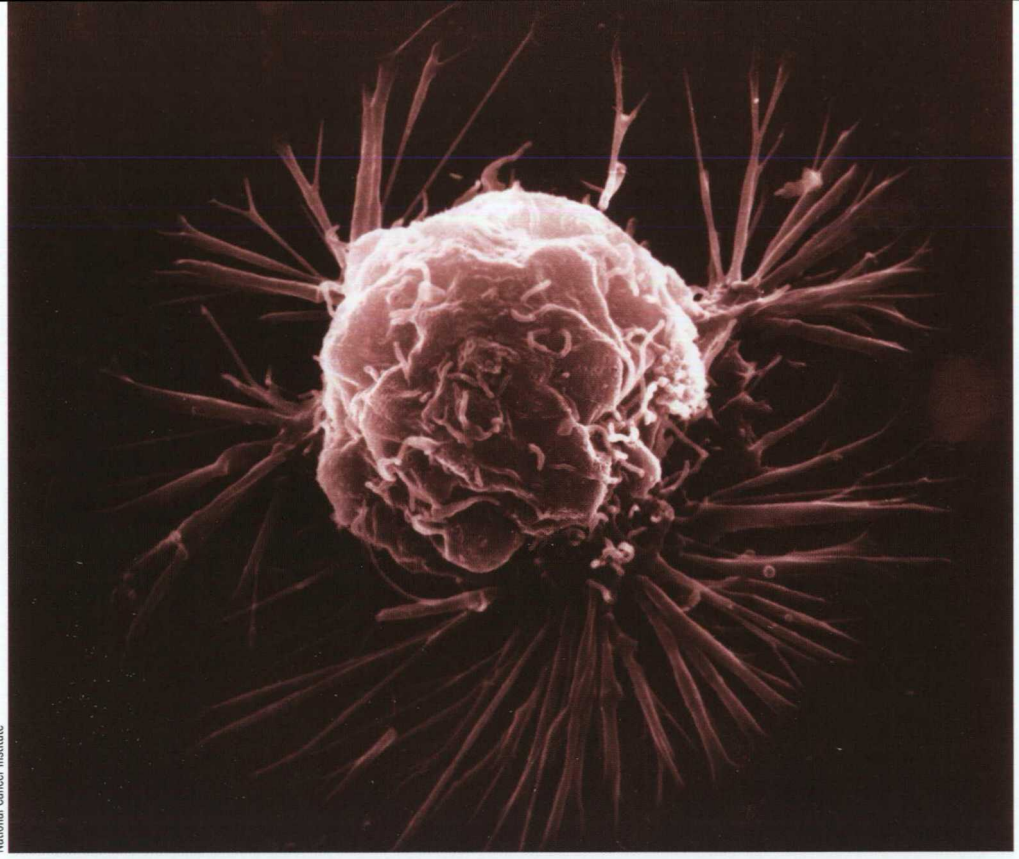
Using genetic counseling (including molecular biology tools) to define the likelihood of developing the disease makes sense when the penetrance is high; this means that the probability of developing cancer due to mutations is high. For a woman carrying the mutated BRCA1 gene, the risk of developing cancer in her lifetime is 70%; however, this risk is around 40% at the age of 40. I am not a doctor and so perhaps shouldn't express an opinion, but it seems to me that preventative mastectomy doesn't make sense if the woman can bear and feed children naturally; the procedure can be put off until it becomes necessary. But of course women with a high predisposition for developing the disease need to undergo regular testing so that appropriate action can be taken immediately if any symptoms appear. Doctors should explain all the therapies available, but the final decision must lie with the patient. When dealing with cancer, it is impossible to avoid surgical intervention, so I believe that the greatest hope lies with regenerative medicine. The idea of simply removing and discarding damaged tissue, followed by replacement of that newly grown from the patient's own cells, is rather elegant. We are already able to regenerate certain tissues, such as cartilage and liver. Repairing genes, however, is extremely difficult; that's not the way forward.

What tools are there in the cancer-fighting arsenal? How does your team's research contribute to this?

Classic chemotherapy acts on the entire body, but damages all cells, not just the cancerous ones. However, we are attempting to selectively block signaling pathways responsible for cancer cell proliferation. This can be achieved using antibodies binding to their corresponding receptors – the first element of the division signaling cascade. Nevertheless, in biology no metabolic pathway exists in isolation. This being a safeguard measure, preventing too many cells from dying. Thus, therapies using inhibitors work only for a while, until the cancer cell starts using an alternative pathway for transmitting signals, and then a new inhibitor must be used.

Medicine is now turning towards biological therapies, such as targeted therapy, genetic therapy, and the increasingly successful immunotherapy. Personalized medicine is also becoming more widely used. For it to be effective, we must first learn about the biology of the given type of cancer and about its interactions with the microenvironment, as well as understanding issues about its heterogeneity and plasticity. In other words, we are some way off from being able to manage cancers effectively. My team conducts research into molecular diagnostics and is developing new tests for selecting those patient subgroups who can gain maximum benefits from a given type of targeted therapy. The new generation therapeutics are very expensive, therefore it is important to carefully select those patients who are to receive them. Administering them to all patients increases treatment costs, however, as well as potentially resulting in side effects, thus making the patient's health condition worse. Basic research is also being aimed at expanding our understanding of the mechanisms inducing carcinogenesis processes.

We are currently focusing on the rare gastrointestinal stromal tumor (GIST). This cancer is driven by mutations in the Kit gene, encoding a surface receptor transmitting proliferation signals. It turns out that the process can be halted using a low molecular weight inhibitor, where the dose depends on the location of the mutation. We have so developed a way of analyzing the gene's status in which every positively identified GIST case treated at the Oncology Centre is then added to a compiled national GIST register by the Department of Soft Tissue, Bone and Skin Cancers. The team studying GIST is now one of the foremost and dynamically growing research groups in Europe, working with numerous institutions both in Poland and abroad. Unfortunately inhibiting the signaling pathway isn't always effective, mainly because it comprises numerous proteins. Blocking the first may not work if subsequent proteins become damaged. This means that it's necessary to test other genes encoding for each protein in the signaling pathway to determine which ones require pharmacological blocking. By using this approach and a carefully selected combination



National Cancer Institute

Breast cancer cell photographed by a scanning microscope, revealing its 3D structure

of therapeutics, we are thereby able to control the cancer for months or even years.
To summarize, we use state-of-the-art molecular diagnostic techniques for early diagnosis of diseases with a genetic predisposition as well as certain cancers. At the same time, drawing upon our understanding of molecular biology and cancer biochemistry, we can personalize therapies for certain groups of patients. Furthermore, in some cases we have a good understanding of how any given genetic damage affects the course of the disease, allowing us to monitor progress.

In 2013, the weekly journal *Science* hailed cancer immunotherapy as its Breakthrough of the Year. What does the method involve?
We have long suspected that the body has some capacity for fighting carcinogenesis, although this ability is limited. As soon as the immune system attacks a tumor, cancer cells try to inhibit the immune response.

So we are dealing with an internal conflict after all?
As I said, it's not a conflict occurring at a level of the entire body, because cancer cells do not intend to cause it harm. Their intention is to survive, so they defend themselves against the immune system. They secrete various substances aiming to deactivate lymphocytes (white blood cells) that destroy foreign or diseased cells. On their surface, cancer cells have tumor antigens, which signal to lymphocytes that something isn't quite right. In most cancers, tumor antigens are poorly defined. In some, such as melanoma and kidney cancer, the case is quite different, which is why in these cancers we occasionally observe spontaneous tumor regression. For most types of cancers, the immune response is too weak to be effective. We have only recently discovered how to enhance the immune system. This new approach to immunotherapy uses the same trick used by tumors to lull lymphocytes into a false sense of security. The therapy stimulates the patient's immune system; lymphocytes "read" the antigens presented on the surface of cancer cells, but to become fully activated, the lymphocytes need another signal. This comes from the co-stimulatory protein B7 found on the surface of cancer cells, which must bind to the CD28 protein on the surface of lymphocytes. To protect themselves against an autoimmune response, the lymphocytes secrete the CTLA-4 protein whose affinity for co-stimulatory proteins is far higher than for the CD28 receptor. By binding to co-stimulatory proteins, CTLA-4 receptors inhibit the activation of T-cells. When this is blocked by antibodies against the CTLA-4 receptor, the lymphocyte can thus freely attack cancer cells, because it now regards them as foreign bodies. The mechanism is rather complex, but it performs extremely well.

There's always just one cell that goes wrong and kicks off the process. Frequently, our body is able to detect it and destroy it. The problem starts when this doesn't happen.
That's right; that's how it always starts. ■

Interview by **Agnieszka Kloch**