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WHAT TUMORS TEACH US

PARALLELS IN CELL AND HUMAN BEHAVIOR

Jana Šmardová

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To my daughters Anna and Daniela

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PARALLELS IN CELL AND HUMAN BEHAVIOR

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A. Introduction

Ethologist and Nobel Prize winner Konrad Lorenz wrote in his book *Civilized Man's Eight Deadly Sins*: "Far from being an insurmountable obstacle to the analysis of the organic system, a pathological disorder is often the key to understanding it. We know of many cases in the history of physiology where a scientist became aware of an important organic system only after a pathological disturbance had caused its disease" (Lorenz, 1974, p. 5). For tumors – currently one of the most common disorders of the human body – this is the perfect truth. Understanding the rules broken by tumors and followed by healthy cells provides an important insight into the fundamentals of healthy multicellular organisms. It is the tumors that remind us how perfectly organized the healthy body is, and how breathtakingly sophisticated is the scenario that makes all these incredibly different, diverse, yet interconnected cells coexist and work together in harmony.

And that is exactly what tumors teach us. Or they can teach it. They show us clearly and painfully what the violation of basic rules means for coexistence and cooperation in the community of cells that make up the multicellular organism. Perhaps they can also teach us something about the rules of coexistence and cooperation in our human community. Or at least, perchance we can get some insightful and playful suggestions to improve or correct the way humans live together and cooperate. In the pages that follow, I will refer to these free analogies as "overlaps."

The development of a tumor begins inconspicuously, just as a cluster of several proliferating cells. Cells that gradually multiply and, step by step, acquire more and more properties that increasingly distinguish them from healthy cells. The pathological behavior of these cells is reminiscent of the behavior of us – humans. Considering the harmonious perfection of a multicellular organism and the dramatic effects of tumor development, one begins to wonder if cancer is really just a disease and a matter of cells. What if cancer represents a more general principle? A more general failure of complex, multi-layered systems? Perhaps tumors thrive not only in our bodies, but also in our lives and in society as a whole. If so, it might be worth investigating whether

the characteristics and behaviors that distinguish tumor cells from healthy cells are not parables or analogs for the characteristics and behaviors of us humans. And do they not then represent such characteristics or behaviors that pose a threat to society as a whole?

It can be argued that simple transfer of knowledge from biological to social systems is foolish, just as the functioning of living systems cannot be explained solely on the basis of understanding physical and chemical processes. This is undoubtedly true.

However, this book does not intend to provide a literal and authoritative transfer of knowledge from biology to the social sciences. It is more like an experiment, a trial, a game. We can use the biological system here as a starting point, as inspiration for analogies and reflections on human behavior. And what is the point? Some do not find one. Some may even see this book as pure nonsense. On the other hand, if only some of the findings about tumors and cancer were more generally applicable, and we were aware of all the limitations and simplifications we are making, the conclusions could be extremely useful to human society. While we already know the consequences of cancer and its effects in cells and multicellular organisms, it is difficult, if not impossible, to assess the behavior of people in society that we might label as "cancerous." We already have a lot of experience with the diagnosis and prognosis of biological tumors. We have developed tools to intervene in their further development and cure them. In contrast, our experience with human "tumor behavior" is very limited. The "overlaps" of biological knowledge with the human world could help us to become more sensitive to the "cancerous behavior" of people, groups, and especially ourselves in our own lives. And awareness of the possible consequences of human cancerous behavior could inspire, stimulate, and motivate us to become less tolerant and supportive of conduct that has bad consequences for ourselves and others. This awareness could help free us from many prejudices and from what we think are the unchangeable conditions of our time.

B. Overlaps

Is it appropriate to think of overlaps?

American writer, theorist, and essayist Susan Sontag would probably disagree. In her book *Illness as a Metaphor: AIDS and its Metaphors*, she writes: "But the modern disease metaphors are all cheap shots. The people who have the real disease are also hardly helped by hearing their disease's name constantly being dropped as the epitome of evil. And the cancer metaphor is particularly crass. It is invariably an encouragement to simplify what is complex and an invitation to self-righteousness, if not fanaticism" (Sontag, 1989, p. 85). Nevertheless, tumors and cancer are used as metaphors. And quite often and in a wide variety of contexts. And this is not a modern phenomenon. Already Publius Ovidius Naso used cancer as a metaphor in his Metamorphoses, written in around 8 AD, in the second book, in a chapter called "Envy and Aglaur":

Strenuous she strives to raise her form erect,
But stiffen'd feels her knees; chill coldness spreads
Through all her toes; and, fled the purple stream,
Her veins turn pallid: cruel cancer thus,
Disease incurable, spreads far and wide,
Sound members adding to the parts diseas'd.
So gradual, o'er her breast the chilling frost
Crept deadly, and the gates of life shut close…
(Ovidius Naso, 1974)

But let us return once again to Susan Sontag. She writes elsewhere in her book: "To describe society as a kind of body, a well-disciplined body ruled by a 'head', has been a dominant metaphor for the polity since the days of Plato and Aristotle, perhaps because of its usefulness in justifying repression… Rudolf Virchow, the founder of cellular pathology, furnishes one of the rare scientifically significant examples of the reverse procedure, using political metaphors to talk about the body. It was the metaphor of the liberal state that Virchow found useful in advancing his theory of

the cell as the fundamental unit of life. However complex their structures, organisms are, first of all, simply 'multicellular' – multicitizened, as it were; the body is a 'republic' or 'unified commonwealth'. Among scientific-rhetoricians Virchow was a maverick, not least because of the politics of his metaphors, which, by mid-nineteenth-century standards, are antiauthoritarian" (Sontag, 1989, pp. 6–7). This raises the question of what is actually the appropriateness of using metaphors. Which ones are acceptable? And when, in what context?

This question has been asked by Bruce H. Lipton, an American biologist and teacher whose research mainly deals with the development of muscle cells. In his book *The Biology of Belief*, he describes his educational experience. "I had been fascinated by the idea that considering cells as 'miniature humans' would make it easier to understand their physiology and behavior," he says. But he is aware of the risks of such a comparison: "Trying to explain the nature of anything not human by relating it to human behavior is called anthropomorphism. 'True' scientists consider anthropomorphism to be something of a deadly sin and ostracize scientists who knowingly employ it in their work" (Lipton, 2005, p. 35). He himself uses the opposite approach in his book, which he calls "cytomorphism" or "subcellularization," and explicitly states that we can learn much from cells. He believes that "cells teach us not only about the mechanisms of life, but also teach us how to live rich, full lives" (Lipton, 2005, p. 27). By conceptualizing his "cytopomorphism," Bruce Lipton fulfills to some degree the ideas and challenges of Carl Richard Woese (1928–2012). Woese was an American microbiologist known for constructing a prokaryotic phylogenetic tree based on sequence comparisons of ribosomal RNA and defining the new kingdom of Archaea. He was involved in introducing the theory of the RNA world and brilliantly interpreted new phenomena in biology throughout his long life. In his extensive essay on the future of biology published in 2004, he wrote: " Biology today is at a crossroads. The molecular paradigm, which so successfully guided the discipline throughout most of the 20th century, is no longer a reliable guide. Biology, therefore, has a choice to make, between the comfortable path of continuing to follow molecular biology's lead or the more invigorating one of seeking of a new and inspiring vision of the living world, one that addresses the major problems in biology that 20th century biology, molecular biology, could not handle and, so avoided. The former course, though highly productive, is certain to turn biology into an engineering discipline. The latter holds the promise of making biology an even more fundamental science, one that, along with physics, probes and defines the nature of reality. This is a choice between a biology that solely does society's bidding and a biology that is society's teacher." He believed that "the main task of biology is to help us understand the world, not to change it. The greatest task of biology is to teach us" (Woese, 2004).

Is it reasonable to think of overlaps?

And is it useful to ask this question? Is it even important to look for an answer to it? Overlaps are not science! And they do not even want to play on it! In this book, the term "overlaps" refers to facts based on the science described in the chapters on tumor biology (Chapters A). Overlaps (Chapters B) are just free analogies, metaphors, ideas, topics to think about, to inspire or to teach. According to Carl Woese, this is the task of the "New" Biology. According to Bruce Lipton, cells have this potential. And perhaps Susan Sontag would accept the overlaps. But who knows? We will not ask her again. She herself died of cancer…

1A. The healthy multicellular organism

The incidence of tumors in humans is not uncommon, nothing rare. It seems that the very basis of the human body, the way it was created and the way it functions, carries the potential for tumor formation.

A healthy multicellular organism is a harmonious community of a large number of cells. Each cell has its function, which it performs at a particular time and place for the maximum benefit of the organism as a whole. The individual cells of the organism are not in competition with each other. On the contrary, they support each other and work together.

The life of every human being begins in the same way: with one cell – a zygote, which is formed by the fusion of two germ cells – sperm and egg. From it, through repeated rounds of cell division and differentiation, gradually develops the embryo, the fetus, the newborn – and the baby then gradually develops and matures into an adult human being (Fig. 1). The body of an adult human is a complicated multicellular system. What do we know about this system?

How many cells are there in the human body?

It is no surprise to anyone that our bodies are made up of a large number of cells. But how many? The bodies of multicellular organisms differ in size and therefore in the number of cells that make them up. From tiny multicellular organisms we can deduce that the number of cells in their adult bodies is not random but on the contrary perfectly regular and accurate. For example, the body of the adult nematode *Caenorhabditis elegans* consists of 959 cells (Potts, Cameron, 2011). Counting the exact number of cells in the body of an adult human is, of course, impossible. In 2013, an Italian-Greek-Spanish research team attempted to make the most serious and rigorous estimate possible. The researchers used a model of an average person – a 30-year-old young adult who weighs 70 kg, is 172 cm tall and has a body surface area of 1.85 m^2. They admitted that the number they calculated is inherently inaccurate and varies from person to person. Their final estimate of the number of cells in the body of an adult

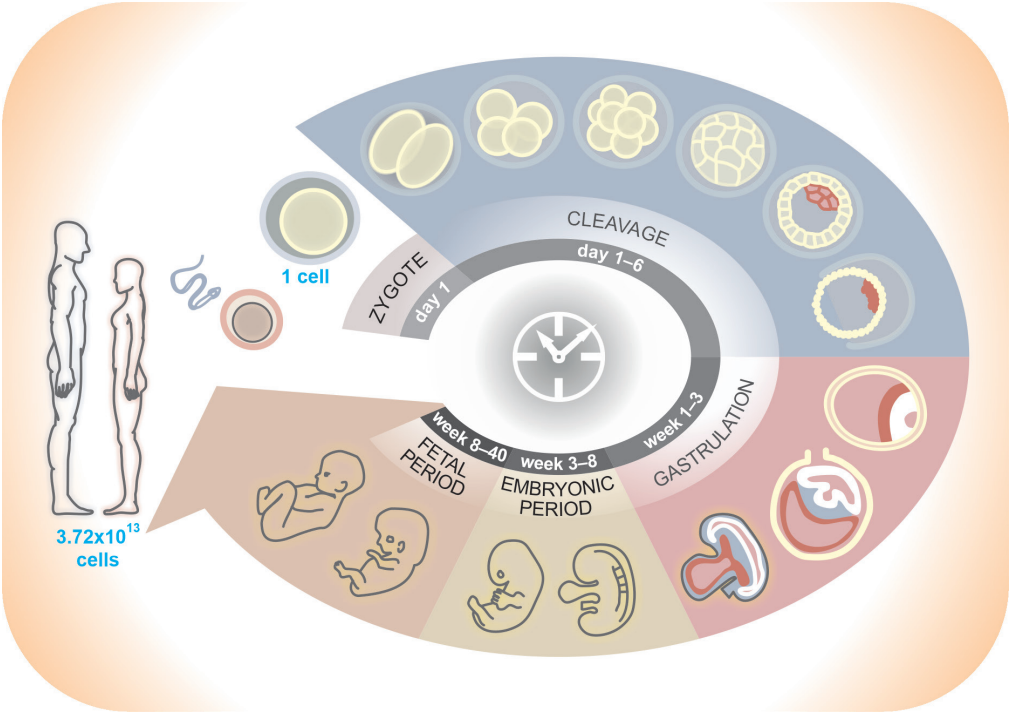

Fig. 1 Development of the human being
The life of a multicellular organism begins with the fusion of egg and sperm into a zygote. It divides again and again, the number of cells increases, the cells gradually differentiate, arrange themselves and form more and more complex structures. The stages of development after fertilization, which last about eight weeks, are called embryogenesis. Around the 56th day of development, when the foundations for all organs have been laid, the human embryo transforms into a fetus and fetogenesis begins. The body of an adult human consists of approximately 3.72 ± 0.81 × 10^{13} cells, which are differentiated into more than 200 different cell types.

human was 3.72 ± 0.81 × 10^{13} (Bianconi et al., 2013). This is a staggering number. Just for comparison, there are nearly 8 billion (7.86 × 10^{9}) people currently living on our planet. This means that there are 5,000 times more cells in each human body than there are people on Earth.

How many different cell types do we have in our bodies?

A typical feature of multicellular organisms is diversification. Cells differentiate into various specialized forms. We are naturally aware of this fact. We know that there are different cells in our body, such as blood cells (of which there are several types), neurons, muscle cells, epithelial cells covering the external and internal surfaces of organs, liver cells, and many others. But how many different types of cells are there in our bodies? The most common estimate is about 200 to 400 types. For example,

the "Cells of the Adult Human Body" catalog published by Garland Science lists 210 clearly distinguishable cell types that can be determined by conventional histological examination techniques: that is, based on microscopic analysis of morphology (shape and structure) and staining. However, this list is not exhaustive as most cell types can be further subdivided into clearly distinguishable subtypes by other methods, e.g. physiological characteristics, degree of differentiation, developmental capacity, and so on. However, even the number 210 is overwhelming and reflects the considerable diversity of cells in our bodies. All these different cells are urgently needed by the body. Each is essential for survival and smooth functioning of the whole. Moreover, each type of cell must be present in a very specific quantity, and even a small deviation from the optimum threatens the viability of the body. Neither a deficiency nor an excess of cell types is tolerated. Deviations from equilibrium in either direction seriously disrupt the harmony of the whole.

A multicellular organism is a highly organized system of different cells

Not even the right amounts of the right types of cells is sufficient for the body to thrive. Also, all cells must be in the right place. Liver cells must not be in the muscles; muscle cells would not serve well in the brain or blood circulation. The nervous system would not be efficient if all the nerve cells were concentrated only in the brain and did not form a network running throughout the body, or if that network was broken somewhere. And the right placement, as well as the right connections – both structural and functional – are much more subtle than the examples given. A closer look at any piece of tissue would show that the order created by the cells in the body is enormous and the tolerance for deviation is low. Every part of the structure must be perfectly placed and arranged.

Considering the large number of cells in the human body, their diversity, and the need for their precise numerical representation and perfect distribution in the organism, two things might interest us. Both are well known, but we are seldom amazed by them. The first is the already mentioned fact that at the beginning of the development of an extensive, highly organized cell community there is always only one fertilized egg (Fig. 1). The nucleus of this cell contains genetic information that largely predetermines the morphology, physiology, and properties of the entire future organism that emerges from it. The second fascinating and also well-known fact is that the individual cells in the body, although so different from each other, all carry almost the same genetic information. This raises extremely interesting questions. How do the individual cell types develop? How do they differentiate? How do they find their place in a complex organism? How does a multicellular organism gradually grow and how is order created? And how is this perfect order maintained throughout the life course? Who or what drives the whole system and its development?

Development of the multicellular organism

Ontogenesis is the process of individual development from the beginning of the embryo until the death of the organism (Fig. 1). The actual beginning of the development of a new individual is fertilization. This is the moment when the germ cells, i.e. the unfertilized egg and the sperm, fuse, resulting in the formation of a fertilized egg or zygote, as mentioned earlier. After fertilization, the egg divides several times. The first division produces two daughter cells, the second produces four, then eight, sixteen, and gradually the number of cells in the developing embryo increases. These first divisions of the zygote are called cleavage. The cells formed at this early stage, the blastomeres, create a structure resembling a mulberry called a morula. A morula is a developmental stage consisting of up to 16 blastomeres. They are in close contact and constantly communicate with each other through a variety of molecular signals. They are similar, function similarly, and send similar signals.

Later, fluid enters the spaces between the blastomeres and the morula develops into the blastocyst. As the number of cells in the embryo increases, the different groups of cells begin to develop differently. Cell division comes under control and the first differentiation takes place. The outer layer of cells, called the trophoblast, surrounds the entire embryo and forms the basis of the future placenta. The embryoblast is an inner cell mass at one pole of the embryo that develops into the new individual being. During the differentiation of the embryoblast, which originally consisted of the same cells, groups of cells are gradually formed that differ from each other and give rise to the so-called germ layers: endoderm, ectoderm and mesoderm. The formation of the germ layers is called gastrulation. A very extensive rearrangement of cells occurs, as the basic orientation plan of the body and the foundations of organs and organ systems are laid (organogenesis). The individual parts of the embryo gradually become more finely specified, and complex tissues are formed, composed of many different types of cells to perform specific functions (histogenesis). While the cells in the morula and blastula still have considerable developmental flexibility and plasticity – they develop according to their position in the embryo – they lose this during gastrulation and acquire a clear and unchanging determination of their fate.

Morphogenesis as a process of formation of body structures has its molecular, cellular and organic levels. At the cellular level, this process includes proliferation, i.e. multiple rounds of cell division; gradual cell differentiation, i.e. diversification and specialization; and also programmed cell death, i.e. termination that accompanies development and occurs at a predictable time and place. At the organ level, cells move and arrange in three dimensions, establishing (and also breaking) mutual physical and functional connections. At the molecular level, these processes correlate with the regulation of gene expression, i.e. the turning of specific genes and gene groups on and off (Vyskot, 1999; Carroll, 2010). Even this brief overview of developmental processes in multicellular organisms raises the question: what drives such a complicated process?

The maintenance of the structure and function of a multicellular organism

The perfection of the multicellular machinery, the interaction and cooperation of cells, does not end with the completion of the organism's development when it reaches adulthood. The multicellular organism has an enormous potential to cope with a number of imbalances and disturbances that may occur during its lifetime due to the external or internal environment. It tends to maintain perfect order. When a part of the body is damaged, the body has a considerable ability to repair or replace the damaged tissue. This repair is usually near perfect, even for injuries that are anything but trivial. We often think of them as trivial because their correction is somehow automatic, without our conscious intervention. Who among us has ever scraped his knee? Even more severely damaged tissue is quickly and completely replaced in a form that is almost indistinguishable from the original tissue. And this is by no means a simply structured tissue. Quite the opposite! It consists of many different cell types that are in the right relationship to each other, correctly aligned and positioned in the tissue and ready to function perfectly.

Cell and tissue regeneration is not just about non-physiological damage. The organism itself is constantly wearing out and consuming some cells. Some of them even very quickly: for example, the cells of the skin surface, intestinal mucosa and more. Other cells wear out more slowly and are replaced only to a very small extent, such as the endothelial cells that make up the lining of blood vessels. Some cells in the body actually function for a lifetime and are almost never replaced. This is the case with the nerve cells, neurons. In any case, in a healthy organism, cells are always replaced at the right time, appropriate rate and in the right places to maintain an optimal structure in the body. So, the question arises again: where and how is all this controlled?

Genome and gene expression profiles

The basic plan and instructions for the development of the whole organism is genetic information stored in chromosomes (Fig. 2), which form the so-called zygote genome. In humans, there are 23 pairs of chromosomes. Twenty-two pairs are the so-called autosomes, and the last pair is the sex chromosomes. In males there are X and Y chromosomes, and in females there are two X chromosomes. Humans have a diploid genome, which means that each gene – with the exception of the genes on the sex chromosomes in males – is present twice in the cell. The human genome contains about 19,000 different genes (Frankish et al., 2019). The zygote, the fertilized egg, contains almost all the genetic information in its genome that is necessary (but not sufficient) for the development of the organism, for its function, and for determining many of its characteristics. Almost all cells, both in the developing and adult organism, contain the same genome, i.e. the same set of identical and equally arranged genes and regulatory sequences.

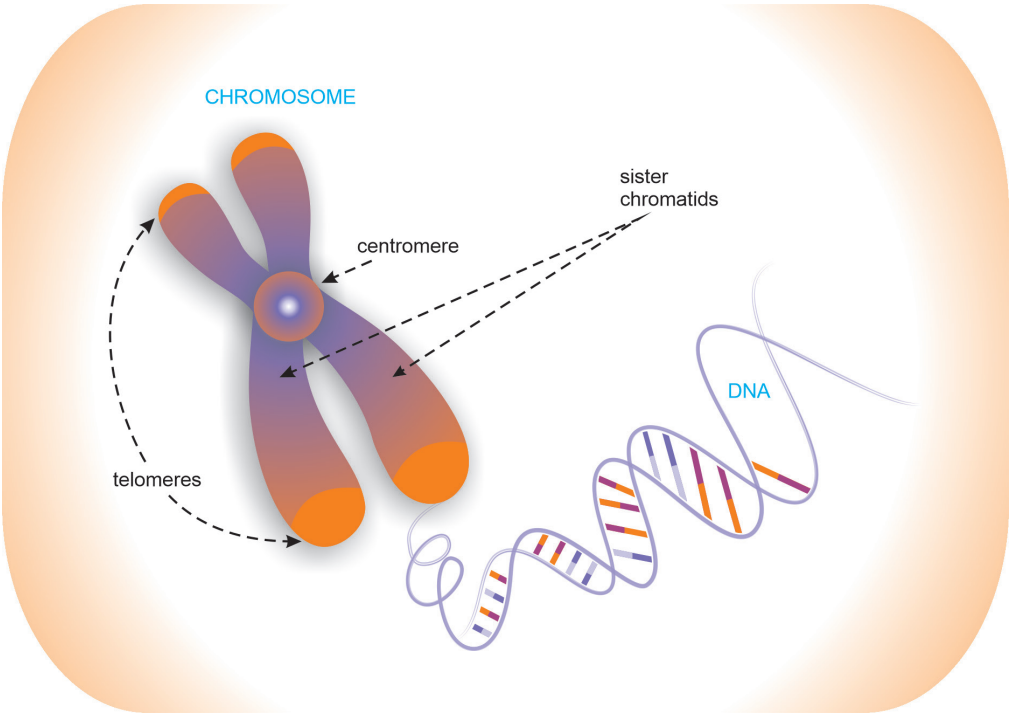

Fig. 2 Chromosome
Chromosomes are special structures located in the cell nucleus. They consist of deoxyribonucleic acid (DNA), which contains genetic information, and proteins. Shown is a condensed, mitotic chromosome with one centromere and two sister chromatids. The ends of the chromosome form telomeres. DNA forms two complementary strands arranged in a double-helical structure that is compact in a mitotic chromosome.

No cell in the body – not even a zygote – actively uses all the genes in its genome. Cells differ significantly in the genes they actively use and the genes that are turned off. An illustrative example is the genes that code for antibodies. Antibodies (immunoglobulins) are glycoproteins that, as part of the immune system of a multicellular organism, are able to recognize and neutralize objects foreign to the organism, known as antigens. Antibodies are produced by a specific type of white blood cells, B lymphocytes. It is clear that the genes that code for antibodies in B lymphocytes are turned on: they are actively expressed to produce their protein products in large quantities. All other cells in the body also have these genes in their genome, but they are turned off. They do not use them. The production of antibodies is the function of B lymphocytes, but not of neurons or muscle cells, for example. On the contrary, the function of a neuron requires a set of proteins that are unnecessary for both lymphocytes and muscle cells. Therefore, a neuron turns on a different set of genes than a lymphocyte or a muscle cell. So, in general, almost all cells in the body have almost the same genome, but they

differ significantly in what are called gene expression profiles, i.e. the configuration of genes that are actively used in the cell and those that are turned off. For the sake of completeness, we should add that there are also genes that code for proteins that are necessary for the basic functions of every cell. They are constantly switched on in all cells and are called housekeeping genes.

Cell differentiation, stem cells and tissue structure

Differentiated cells are the basis of the tissues and organs of the adult organism. They perform specialized functions necessary for maintaining the function of a particular tissue and organ. These include the aforementioned lymphocytes and other blood cells, neurons, muscle cells, and many other cell types, totaling about 210 types. In addition, there are always undifferentiated and poorly differentiated cells, often referred to as supply cells. These include stem and progenitor cells. They give rise to the differentiated cells (Fig. 3). By general definition, stem cells are those which, when they divide, give rise to a copy of themselves (they have the capacity for self-renewal) and another more differentiated cell.

If a cell can give rise to all cell types of the embryo and adult, including germ cells (oocytes and spermatozoa) as well as extraembryonic structures, such as the placenta, we call it totipotent. For example, a fertilized egg and early blastomeres are totipotent. Cells that have all of the above characteristics except the ability to form extraembryonic structures are called pluripotent. Embryonic stem cells are pluripotent. All other stem cells found in specialized tissues of the embryo and adult are multipotent, meaning they are capable of forming multiple cell types, but not all, or unipotent, meaning they form only one cell type. More specialized stem-like cells are called progenitor cells. These can be multipotent or unipotent. A prerequisite for "stemness" is the ability to self-renew, i.e. after each division of the stem cell, at least one daughter cell retains the original characteristics of the parent stem cell. The daughter cell that loses this ability becomes a differentiated cell. This specialized cell produces all the proteins required for its specialized function. It may divide several times or not divide at all. Under normal circumstances, a differentiated cell cannot turn back into a progenitor or stem cell; differentiation is a one-way process.

Shortly after fertilization of the egg and the first three cycles of cell division, totipotent cells disappear and are replaced by pluripotent cells of the inner germ layers and multipotent cells of the outer germ layer. In the organs and tissues of the adult organism there is only a small supply of adult stem cells. Normally, they live here peacefully, without profound activity, but they have the potential to divide and differentiate when needed. The range of potential cell types that can arise from a given multipotent stem cell in the adult body is usually limited to those found in tissue. For example, hematopoietic stem cells in bone marrow can give rise to all the cells that make up blood, but not nerve, intestinal, or insulin-producing cells (Fig. 3). Although almost

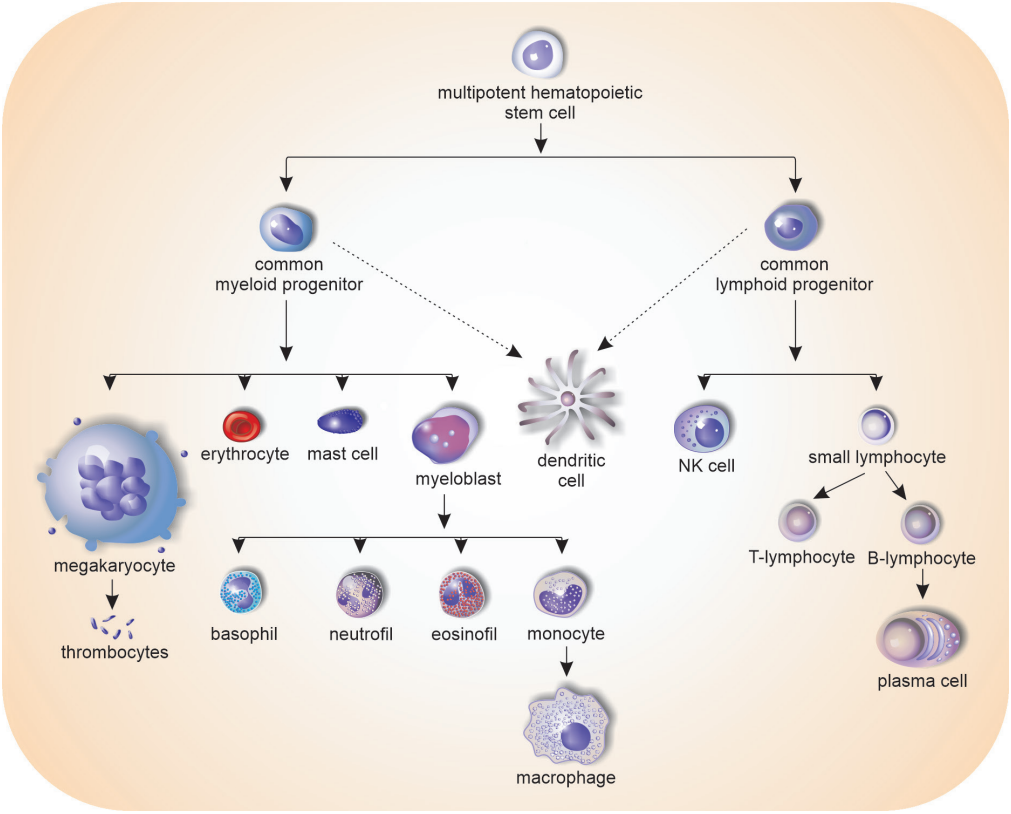

Fig. 3 Cell differentiation
An example of cell differentiation is the process by which immature, unspecialized stem cells gradually give rise to structurally and functionally specialized cells: hematopoiesis, the process of forming mature, fully differentiated blood cells and cells of the immune system. They arise by gradual differentiation from a multipotent hematopoietic stem cell via myeloid and lymphoid progenitor cells.

all cells in the body possess a complete genome, i.e. the genetic information required for the differentiation and development of each specialized cell, most somatic cells are restricted in their development to a certain spectrum of possible phenotypes.

How do cells communicate? Signaling pathways

In a multicellular organism, cells communicate constantly and intensively with each other. Even the blastomeres, which are formed when the fertilized egg undergoes cleavage, immediately begin to communicate. The exchange of signals between cells is necessary for the successful development of the organism. They learn their position and place in the organism, they share tasks and differentiate. But even in a mature organism, intercellular communication is essential for daily physiology. The textbook

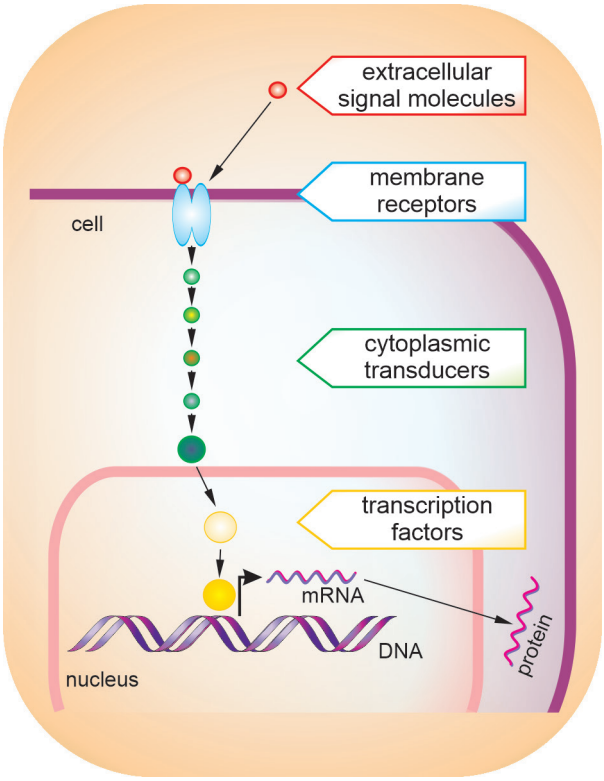

Fig. 4 Common signaling pathways
The receptor located in the cytoplasmic membrane of the cell is activated by the extracellular signal molecule and transmits the signal to the interior of the cell. The signal is then relayed by cytoplasmic carriers to an effector, such as a transcription factor, which can turn its target gene(s) on or off.

Essential Cell Biology states: "As in any busy community, there is a constant hub-hub of communication (in a multicellular organism): neighbors carry on private conversations, public announcements are broadcast to the whole population, urgent messages are delivered from distant sites to individuals, alarms are rung when danger threatens…" (Alberts et al., 1998, p. 481). Cells can communicate with each other directly, when they transmit signals through cellular connections, or indirectly, by releasing extracellular signaling molecules.

What is a signal? And how does the cell respond to it? What is a signaling pathway? In general, we can say that the signaling pathway consists of several points: (1) the extracellular signal molecule, (2) the receptor in the cell membrane, (3) the cytoplasmic signal transducer, and (4) the effector (Fig. 4). The extracellular signal is a molecule – a growth factor, a hormone, a cytokine, an amino acid and similar molecules – located in the extracellular space. Only those cells that are equipped with a suitable receptor

for the signal on their surface respond to it. Cells lacking this receptor cannot respond to the signal, even if it is in their immediate vicinity. A receptor is a molecule that is usually located in the cell membrane (a transmembrane receptor). Its extracellular part is directed outward from the cell, while its intracellular part is directed into the cell. The extracellular part of the receptor is responsible for the recognition and binding of the signal molecule.

Where do signals originate, where do they come from? Signaling molecules are produced by cells. A particular signal molecule may be produced directly by the cell, which then responds to it. This is an autocrine type of signaling because it is a type of auto-signaling ("cellular self-talk"). The cell sends a signal and responds to it itself. Paracrine signaling is much more common. This involves signals that originate from a producing cell and affect other cells in its immediate vicinity rather than the cell itself. In endocrine signaling, the signal originates from cells that are very distant from the effector cells. An example of this is the hormone produced by an endocrine gland. The hormone may be secreted and distributed throughout the body or in a large part of the body, stimulating many cells of different types, often very distant from a particular gland. Also in this case, only those cells that have corresponding specific receptors on their surface can respond to the particular hormone.

After the binding of the signal molecule to the extracellular part of the receptor, the receptor changes the structure of its intracellular part. As a result, the signal is transmitted to the interior of the cell. The altered structure enables the receptor to transmit a signal to another molecule inside the cell. This molecule can pass it on to another molecule, and thus the signal can travel through a chain of carriers to finally reach the effector that triggers the cell's response. Signaling pathways can vary in length, branching and cross-talking. Signals can be amplified, attenuated, modulated, and integrated, i.e. combined with other signals (Fig. 5). This means that even if the same signal molecule is recognized by the same receptors in different cells, the response of these cells can be very different, depending on their specific equipment, i.e. their system of transmitters and effectors.

The cell may have a variety of receptors on its surface that decide which signals from the external environment it will respond to. Cells differ from each another in the composition of surface receptors, as well as in the composition of intracellular transporters and, in general, many other molecules. The difference can be small, as in developmentally related, similar cell types (e.g. mature and immature white blood cells), or significant, as in cells that are very far apart (e.g. a blood cell and a neuron). On the other hand, very different cells may carry the same or similar surface receptors and thus respond to the same (e.g. endocrine) signals. Let us not forget that all body cells have almost the same genetic information in their nucleus. The differentiation of cells is related to their development, i.e. to their individual history, to the experiences that caused each cell to use a different set of its genes. One of the possible outcomes of

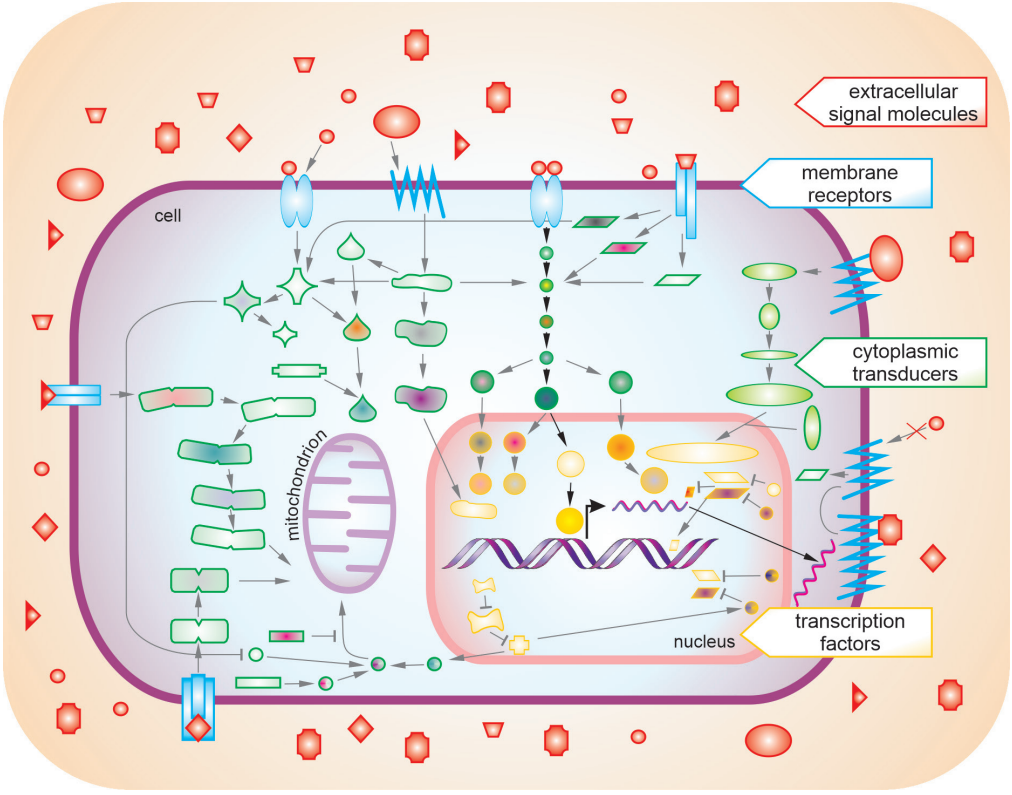

Fig. 5 Signaling cascades
In each cell, there are many different signaling pathways that vary in length, branching, crossing and intertwining. Thus, signals can be amplified, attenuated, modulated, combined and integrated.

signaling events in cells is the turning on or off of a particular gene or group of genes. One could also say that the acquisition of a new experience changes the cell and this change can more or less affect how it will respond to other stimuli, other signals, from then on.

We have described the signaling pathway as a sequence: extracellular signal – transmembrane receptor – cytoplasmic transporter – effector (Fig. 4). This is a very general scheme that has many variants. We have already seen that the spectrum of what can be an extracellular signal is relatively broad. Moreover, the signal need not always be extracellular. The cell is constantly monitoring its own internal environment, its own state, and naturally responds immediately to any imbalance, any deviation from the optimal state. It maintains homeostasis. Signaling pathways are not clearly defined linear pathways, but rather signaling networks: they branch out in different ways, intertwine, talk to each other, and interact with each other (Fig. 5). The end result of the signaling pathway can also be diverse and complex, triggering multiple parallel

events. The spectrum of effectors is also large. It includes the aforementioned gene regulation, leading to the expression or silencing of various genes, as well as regulation of metabolism, alteration of the cytoskeleton or other cell structures.

Who controls a multicellular organism?

The structure and function of a multicellular organism is complex. The human body consists of a huge number of many different and perfectly arranged cells. This highly complicated and precise structure develops from a single cell and is extremely stable throughout the lifetime of a human being. Who or what controls all this? Who controls and ensures that the right cells are in the right place to differentiate into the right cell types and perform their proper functions for the benefit of the entire organism? Where and how are these important decisions made in the body?

There are basically only two possibilities. Either there is a "control center," which supervises the entire multicellular organism, assesses its condition, controls and coordinates the individual organs, tissues and cells, and ensures that they work for the benefit of the entire organism, or there is no such control center, and conversely, each cell is responsible for its harmonious integration into the function of the entire body and assumes full responsibility for its own condition, and to a reasonable extent (about 10^{-13} to 10^{-14}), for the condition and fate of the entire organism as well.

Thinking about the extraordinary complexity of the arrangement of the human body and being aware of the low tolerance of any imperfection in this arrangement, one would not even like to believe that the second option is correct! The existence of a control center that gives instructions, advice or commands to individual cells on what to do and how to behave in the body has not been proven. Quite the contrary. Individual cells and groups of cells work largely autonomously. However, they constantly communicate with each other and influence each other (Weinberg, 1998). Each cell constantly monitors its own state and communicates it to surrounding cells. At the same time, it constantly monitors and responds to its environment – the state of neighboring cells and the non-cellular microenvironment. This information is immediately perceived and processed for an appropriate response. This exchange of information takes place constantly. All changes and fluctuations in the state can be continuously reflected and balanced. In this way, equilibrium, homeostasis, is maintained. Without central authoritative control, the cells act quite independently, "from below," and in a coordinated way they create and maintain a perfect multicellular organism.

1B. Systems

What is the system?

A multicellular organism is a highly organized system of differentiated cells. By definition, a system is a complex consisting of parts that interact with each other. Flows of information, matter, and energy can occur between the parts of the system. Thus, a system is not just a set of parts; its quality is not simply the sum of the qualitative contributions of the individual parts. Mutual bonds and relationships develop among the components of the system, and the resulting quality is largely determined and reinforced by the relationships among the individual components of the system, their cross-links, organization, and cooperation.

General systems theory

The foundations of systems theory were laid in the mid-20th century by Ludwig von Bertalanffy, a biologist and philosopher. Systems theory is not concerned with the laws studied by particular scientific disciplines such as physics, biology, economics, sociology, and others, but seeks to understand and explain the principles of phenomena common to these objects. It focuses on the laws common to various living and social systems. It assumes that certain general principles apply to different systems, regardless of their nature. This is a very important idea and a very important concept, because recognizing, naming, and grasping such general principles and laws in one or more systems would allow their application to other systems as well. It would not be necessary to rediscover the same principle repeatedly in different isolated domains. General systems theory thus provides an ideal conceptual framework for unifying the various scientific disciplines and is a tool for transferring principles from one domain to another. Similarly, it provides a conceptual framework for the "overlaps" in this book.

In transferring knowledge from one system to another, it is obviously necessary to avoid superficial, simplistic analogies. Systems are very different, varying in complexity and hierarchies. There are so-called emergent properties, i.e. properties that occur at a certain level of complexity but do not exist at the system level of lower complexity.

Therefore, one cannot automatically assume that what is true for a system with a lower hierarchy is also true for a system with a higher hierarchy. Thus, the findings and conclusions from the biological system cannot simply be applied to the social system. This is not the correct approach. The human community system clearly has a different level of complexity than a system of organisms consisting of cells. Humans have many purely human characteristics and capabilities that are not found in cells. Human society is more complex than a community of cells. Yet Bertalanffy's systems theory is the bridge that connects research from different disciplines. Equipped with "overlaps" we can also proceed and cross this bridge.

Is bottom-up management a common feature of systems? The hive as superorganism

In multicellular organisms, the existence of a control center from which the individual cells in the body receive instructions, advice, or commands about what to do and how to behave has not been established. On the contrary, the individual cells operate largely autonomously and independently and, thanks to constant communication and mutual influence, are able to form a coordinated, well-functioning complex, a system. Is this networked and interconnected but highly autonomous behavior of the individual parts a general feature of living systems?

Phenomenal Bees: Biology of Bee Colony as a Superorganism is the title of Jürgen Tautz's book on the honey bee (Tautz, 2009). In it, he explains that the general tendency of evolution to create increasingly complex structures has produced multicellular organisms that have evolved into a superorganism. Superorganisms (e.g. bee colonies, hives) arise from the union of independent organisms and represent a new level of complexity. As a result, the world of living organisms acquires completely new possibilities. For example, a bee colony as a single biological unit can make decisions that are inaccessible to individual bees. The bee colony as a superorganism is an adaptable complex community of living beings consisting of many thousands of individuals that are constantly active and can adapt to the conditions of their environment and the activities of their colleagues in the nest. The overall behavior of the bee colony is not controlled by a superior authority, but is the result of cooperation and competition among the bees. Tautz gives several concrete examples of the functioning of the bee colony that correspond to this arrangement.

An example is cost optimization according to the clutch supply. In other words: how do bees figure out where to fly and where to collect pollen and nectar so that the distance to the source, and thus the cost, is balanced with the gain, i.e. the quantity and quality of pollen collected? He writes: " No bee from the hive can oversee supply and demand and perform the task of labor distribution. And yet we know from observations and experiments that the bee colony optimally distributes the labor force in space. How is this possible if no one in the colony knows about the overall situation? From a purely technical point of view, the solution lies in a decentralized, self-organizing

distribution mechanism. Decentralized means that there is no authority to say 'where the hook is'. Self-organizing means that the pattern of labor distribution used by the superorganism is self-generating, thanks to the many close contacts between individual bees. These contacts are used to exchange information about millions of flowers in the wild. The superorganism stretches its net over more than 100 km^2, pulling it in where it is profitable, and letting it go where there is nothing to gain. The flying bees, which make up about 5–20% of the bees in the colony, are constantly on the lookout for new food sources and then inform their friends in the nest about their new discoveries" (Tautz, 2009, pp. 73–74).

Other examples of the same principle are honeycomb construction, nest hygiene and air-conditioning. Bees have very effective methods of temperature control. They lower the temperature by bringing in water and creating a draft, and they raise the temperature by producing heat using the pectoral muscle. But how do bees manage to correctly set not only the direction of change (i.e. cooling or heating), but also the exact target temperatures? How does the colony activate just the right number of bees to compensate for unwanted temperature fluctuations? There is a simple but very effective trick based on the fact that different bees react differently to a stimulus. Some bees begin to fan (cool) at even a very small rise in temperature. If this first ventilation effort brings the overheating under control, the problem is solved. However, if it fails to do so and the temperature continues to rise, other bees with the next higher sensitivity threshold respond and also create a draft. And so on, as bees with higher and higher sensitivity thresholds are gradually involved. When the temperature finally begins to drop, the first bees stop cooling (the bees with the highest sensitivity threshold, the last to become active). Gradually, more ventilation commands follow with a lower and lower sensitivity threshold. This strategy is very economical, because only as many controllers are directly activated as corresponds to the intensity of the problem. A prerequisite for such a strategy is the presence of reserves composed of different groups of bees. It is this variety and diversity of bees that enables the superorganism to always respond appropriately to current problems (Tautz, 2009).

Thus, a similar principle applies to the bee superorganism as to the multicellular organism: the decision is not made by a control center, but is the result of communication between different parts of the system – the bees in the hive, and the cells in a multicellular organism. Moreover, the example of temperature control shows how important the diversity, the individuality, of each bee is. If all bees were the same and reacted to the same stimuli in the same way, a gradual, gentle and very precise reaction of the superorganism would not be possible. There is nothing left but to exclaim: the glory of diversity!

Glory to uniqueness!

The human genome contains approximately 19,000 genes (Frankish et al., 2019), of which 6.7% are heterozygous. This means that on average, each human has two different alleles in 1,273 of their genes, while the remaining 93.3% of genes have two identical alleles. During the development of haploid gametes (eggs and sperm), up to 2^{1273} (i.e. 10^{383}) different types of germ cells with a unique combination of gene variants can be produced. This is, of course, many more possibilities than a human can generate and use in subsequent generations, but also a much higher number than all that humans have hitherto used during the entire existence of mankind. This means that of the total number of people living on Earth now, in the past, and that can be expected in the near or far future, no two people (except identical twins) are genetically identical (Relichová, 2009). Each of us carries a completely unique combination of genes in our genome, each of us is a completely unique original that is also the only one capable of exploring this unique part of humanity. With our death, this possibility will be closed forever. And so only each of us can and must explore and unfold our unique potential, in more poetic terms, fulfill the meaning of our own lives.

How to find a place in life? About communication I

How to fulfill the meaning of a unique human life? How do we find the right place in life? How do we find out who we are and what is the right place for us? Perhaps we will look for answers to these questions in this book. Maybe the following chapters about tumor cells and tumors will help us to see more clearly and sharply who we are and who we want to be, and who we do not want to be. But we already know some important information about the circumstances we find ourselves in. Systems operate without any central control. There are no instructions or messages from any center about what we should be and what we should do. We resemble specific cells in their specific places in the body, each in its specific microenvironment, which consists of both specific and variable material equipment and specific and variable signal structure and information. We too live in our specific locations, we are endowed not only with specific and unique genetic information, but also with specific and unique life experiences that arise from our own microenvironment and adaptations in response to environmental variability. In order to be one of these optimally functioning cells, a well-functioning component in a system in a way that is personally fulfilling and at the same time in harmony with the overall complex, we must constantly communicate truthfully: carefully and accurately perceive all signals coming from our internal and external environments, and constantly respond appropriately. This means that we must change ourselves ("turn some of our genes on and off", develop, differentiate) and also contribute to the change of our microenvironment (constantly provide information about ourselves as accurately as possible to others). And in this way – like the cells (and the bees…) – we must proceed truthfully, respecting our uniqueness and not being afraid of differences.

2A. The multicellular organism: A system that can create cancer

What is cancer, tumor, carcinogenesis?

Cancer – or malignant tumor disease – is a diverse group of diseases with a common root. A tumor is a pathological tissue that grows and develops without control. It develops in a multicellular organism, but is not coordinated with it, does not benefit it and does not serve its interests. The process of tumor formation and development is called carcinogenesis.

Basic features of carcinogenesis

In the previous chapter we indicated that there is no control center in the body that monitors the entire system and, based on the information thus obtained, sends instructions to individual cells or groups of cells to direct how they should function and behave. Cells have a high degree of autonomy and individual responsibility. This arrangement brings undeniable advantages to a multicellular organism – if it were not practical and functional, such a method of multicellular control would not have prevailed during evolution – but it also has some weaknesses. When cells are not directed and controlled authoritatively from a center and have a considerable degree of autonomy, some of them can go their own way. This allows such a cell to live and develop, but without supporting the organism as a whole. The perfect representative of such a cell which does not cooperate with the organism and pursues only its own interests, is a tumor cell. Tumor cells are sometimes said to violate essential rules of social behavior, and sometimes they are called selfish cells. A single cell that misbehaves does not pose a serious threat to the organism. A potentially dangerous situation arises when such a cell is able to survive and divide because of a genetic change, giving rise to daughter cells with the same genetic change and the same antisocial behavior. The tissue organization or even the entire organism may be infiltrated by the gradually spreading abnormal cell clone.