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Catalans

Oncologia a principis del segle XXI

Oncology at the turn of the 21st century

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Palau de la Música Catalana
Barcelona, 16 d'octubre de 2006

IECentanys1907 2007

Biblioteca de Catalunya. Dades CIP

Massagué i Solé, Joan
Oncologia a principis del segle XXI = Oncology at the turn of the 21st century : conferència inaugural del centenari de l'Institut d'Estudis Catalans, Barcelona, 16 d'octubre de 2006
Text en català i anglès
ISBN 84-7283-866-8
I. Institut d'Estudis Catalans II. Títol
III. Títol: Oncology at the turn of the 21st century
1. Oncologia 2. Càncer — Investigació
616-006.6

Carrer del Carme, 47. 08001 Barcelona

Primera edició: octubre de 2006
Tiratge: 1.500 exemplars

Disseny gràfic: Zink comunicació

Imprès a ALTÉS arts gràfiques, SL
Carrer de Cobalt, 160. 08907 L'Hospitalet de Llobregat

ISBN: 84-7283-866-8
Dipòsit Legal: B. 46057-2006

Recent advances in cancer research have revealed previously impenetrable secrets about the origin and development of tumors. New medicines resulting from this progress have rendered harmless certain forms of cancer that once were lethal. But these clinical benefits, while tangible, are still minimal. What is required, then, to achieve control over cancer in the coming decades? Clearly a greater integration is needed between laboratory investigators and clinical experts. But to make the current promise a reality we need above all social, cultural and political attitudes that will facilitate the integration of scientific ethics into everyday life and the national interest.

At two turns of century

At the turn of the twentieth century, when Prat de la Riba and his colleagues were debating the idea of creating the Institut d'Estudis Catalans (Institute of Catalan Studies), the oncologists of the time were also holding their own debate. Theirs was about the most worrying aspect of cancer, namely the dispersion of the tumor to vital organs, known as *metastasis*. Intrigued by the differing behavior of different tumors in this regard, the British surgeon Stephen Paget had recently proposed the theory of «the seed and the soil». As he saw it, the malignant cells that escape from tumor (the «seeds») colonize those tissues (the «soils») that are propitious for them because of mutual compatibilities. For example, Paget imagined that breast tumors metastasize in the bones and liver, rather than in the spleen, because bone marrow and liver tissues must provide optimal

conditions for the multiplication of breast cancer cells. This quite reasonable view was to meet with stiff opposition. The oncologist James Ewing, of the New York Memorial Hospital, refuted Paget's ideas with a weighty argument. The distribution of the metastases depends principally on the routes of dissemination of the tumor, Ewing said. So, colon tumors metastasize principally to the liver because the liver is the first organ visited by the circulating blood coming from the intestines. For Ewing, the mechanics of tumor cells trapped in the capillaries was a more palpable reality than the soil factors imagined by Paget. The debate was heated and was not resolved until a century later we have seen that both Paget and Ewing were right!

With the benefit of decades of investment in research, the oncologists of the early twenty-first century are rapidly clearing up the mysteries of cancer. At the same time as new knowledge is being acquired diagnostic techniques have come into being that make it possible to identify the presence of tumors while these are still in an incipient state and are easier to eliminate. Progressive improvements in the classic methods of intervention—surgery, radiotherapy and chemotherapy—have considerably reduced the mortality in certain forms of cancer. Drugs that are known collectively as *chemotherapy*, which are effective but suffer from a lack of specificity, are now being replaced, or at least complemented, by compounds that are specifically designed against particular tumor weak points. The first successes of these therapies, the genetic book opened up by the recent sequencing of the human genome, and in general the coming together of a number of disciplines against cancer, are remarkable elements of a perspective that presents formidable opportunities. The roots of this process are to be found in the emergence of molecular oncology during the 1970s, and the investment made by some governments, philanthropists and industries in this scientific challenge.

The flourishing of molecular oncology

Advances in biology often come about from the study of biological rarities. The extreme case of avian sarcomas transmitted in chickens by the virus discovered by Peyton Rous in New York early in the twentieth century led decades later to the discovery by John Michael Bishop and Harold Elliot Varmus about the origin of the *oncogenes* or genes that cause cancer. It turned out that the oncogenes are altered versions of otherwise normal genes of the human genome. This discovery was followed by many other similar ones establishing that cancer is a disease that arises from alterations in the genome. That is to say, cancer is a genetically-based disease.

The fact that cancer has a genetic basis does not necessarily mean that cancer is an inherited disease. The inheritance of strong predispositions to certain cancers is a known fact, but is rare in the human population. The large majority of oncogenic mutations that cause tumors in humans are not inherited but are acquired accidentally in just a few of the billions of cells that make up the human body. Our cells can acquire mutations accidentally when they are exposed to external chemical agents (for example, tobacco smoke) or to physical ones (for example, ultraviolet solar radiation). Oncogenic mutations can also be acquired as a result of errors made by the cells themselves during the process of copying and recopying their genome when they multiply to keep tissues alive.

Whether they are acquired by the effect of external agents, by internal errors, or by hereditary transmission, oncogenic mutations form the basis of cancer. For that reason, the oncologists of the last quarter of the twentieth century began scrutinizing cancers at the molecular level. The identification of mutated genes and of the altered proteins that these genes encode became the collective obsession of this field. These efforts have revealed the role of many of these molecules in various types of cancer as well as their normal function in healthy

tissues. Inevitably, this new knowledge has also begun to show itself in clinical benefits, and one example of this is famous case of Gleevec.

The great little triumph of the drug Gleevec

Leukemias are cancerous diseases of blood cells. There are many kinds of leukemia depending on the type of blood cell affected and the oncogenic mutations at play. One of the most serious leukemias, which was incurable until not long ago, is chronic myeloid leukemia or CML. The diagnosis of CML is based on the presence of the Philadelphia chromosome in the cancerous cells. This aberrant chromosome was described in 1960 by a group of oncologists from that city. They noticed that the CML cells presented the normal number of 23 pairs of chromosomes, but that chromosome 22 had a strange shape. This alteration was due to a blending of the genetic material with chromosome 9. With the advent of molecular technology, it was discovered in the 1980s that this chromosomal «translocation» results in the formation of a hybrid gene. The product of this is the BCR-ABL protein, formed by the «head» of the normal BCR protein and the «tail» of the normal ABL protein. Normally ABL functions as an enzymatic protein that controls cell division in a balanced way. But, in the abnormal context of the product of BCR-ABL fusion, the ABL portion acquires an enormous activity and causes the endless multiplication of white blood cell precursors. A leukemia ensues.

Gradually but effectively, these laboratory results were translated into an almost miraculous cure. In the mid-1990s, chemists at a pharmaceutical company found that one of their synthetic products was active against BCR-ABL in the test tube. Because this was a rare leukemia (fewer than a hundred cases diagnosed annually in Catalonia), the possible new remedy had little prospect of a sizeable market. Nonetheless, the enthusiasm of external investigators

convinced the company to go ahead with clinical trials of the new drug in patients in 1999. The results showed an spectacular effectiveness against CML, and low toxicity, forcing in 2001 the immediate approval of the new drug, now known as Gleevec.

One of the great fears in treating cancer is that any residual tumor remaining after treatment may acquire resistance to the drug and eventually relapse, now with impunity against the treatment. In fact, this happens in CML patients after one or two years of treatment with Gleevec. But research and knowledge have triumphed once again. Foreseeing this problem, oncologists were able to quickly identify the resistance mechanisms and develop, test and put into clinical practice a second generation of drugs that protects against resistance to Gleevec. At the same time, Gleevec has found new indications in other previously incurable cancers, for example a particular kind of gastric tumor. And, the market for Gleevec is not as small as it once looked: the annual sales of Gleevec today surpass €2,000M.

Despite this rosy story, it must be said that Gleevec represents the exception and not the rule in the fight against cancer. Most tumors have a much more complicated biology than CML, and thus demand a more difficult therapeutic strategy. CML is caused by a single oncogenic alteration, the formation of the oncogene BCR-ABL, whereas many other kinds of cancer, including the most common ones, are the result of a progressive accumulation of mutations in different genes of a single cell. Unlike BCR-ABL, most oncogenes in isolation do not cause cancer. Multiple cell surveillance mechanisms ensure the elimination of cells that show a suspicious behavior. In order to cause an overt oncogenic state, most types of cells must accumulate multiple mutations until they overcome all these control mechanisms. It is very difficult for a healthy cell to become cancerous. But when it does, that cell turns into a complex and dangerous delinquent. Taking a sociological perspective on cell behavior is helpful in making this point.

Cell sociology: urbanity, terrorism and cancer

Hundreds of millions of years ago, some single-cell organisms began to find it useful to gather together in colonies with some degree of organization. Living in society proved advantageous in facing up to harsh environments. But this communal life meant giving up certain degrees of freedom. For example, it was socially unacceptable for a cell in the community to divide or move just as it wished. Such decisions were subject to the consensus of the neighbors, which used molecular signals to influence the behavior of each cell for the common good. This form of dialog between cells has been developing and enriching itself over millions of years. A good part of our 25,000 genes are engaged in this task. Molecules known as *hormones*, *growth factors*, *receptors*, *mediators* or *regulators* constitute the information and response network that keeps order among the cells of our tissues. Understanding how this network works to control cell division is a fascinating topic, and a major objective of much current research.

Another major objective is to find out how this dialog fails in cancer. Basically, cancer is the result of genetic alterations in a few cells that make them disobey essential rules of life in community. The cancerous cells increasingly misuse proliferative stimuli and ignore the rules of moderation. Their interaction with their neighbors becomes openly antisocial and delinquent. They avert the policing action of the immune system. Eventually, they break through the physical barriers that encapsulate the tumor, setting out on the sinister march that will sow tumorous cells throughout the body. This then gives rise to cancer colonies in vital organs, or metastasis. Like terrorists at a distance, these colonies represent the culmination of the antisocial and highly lethal evolution of cancerous cells. Fighting metastases is thus a great challenge in the fight against cancer. Unlike the case of Gleevec against CML, the fight against metastasis is going to require combinations of multiple drugs applied in a personalized way according to the profile of the disease in each patient.

Metastasis

How tumors spread and kill remains an enigma, but not for lack of attention. For over a century cancer biologists have entertained the idea that metastasis results from the interplay of wandering tumor cells with permissive target tissues. Yet, decades of scrutiny into the molecular bases of cancer have largely focused on what causes oncogenic transformation and incipient tumor emergence while only skirting the more complex question of how tumor cells take steps towards metastasis: how they meddle with their microenvironment, enter the circulation and succeed in colonizing a distant organ. Progressively, however, the reality that tumors are more than just a mass of transformed cells has struck the field at large. A renewed focus on the problem of metastasis is now apparent, and for good reason: Metastasis remains the cause of 90% of deaths from solid tumors.

Metastasis is a complex problem of cell biology complicated by an acute problem of genetics. Metastatic lesions develop by adaptation of genetically unstable tumor cells to a non-receptive environment. This adaptation involves a selection of advantageous traits in the cancer cells and a necessary recruitment of accommodating traits in the colonized stroma. The capacity of a tumor to spawn cells capable of such behavior may require full-blown oncogenic transformation but can occur when the tumor is still of minuscule size. The origins and nature of these traits are challenging problems, but recent conceptual and technological advances are opening doors for their resolution at last. A conceptual framework for these advances takes advantage of Darwin and his ideas about evolution.

Darwinian evolution of tumors

An underlying concept in our analysis is that metastasis emerges from the evolution of a genetically diversified cancer cell population under the selective pressures of an environment that imposes tight rules on cell behavior. In essence, this explains why millions of cells may be released by a tumor into the circulation daily, but only a tiny minority of these cells will ever manage to colonize a distant organ. The extreme inefficiency of the metastatic process implies a marked environmental hostility against invading tumor cells on the part of healthy tissues. This is not surprising. The genome of a highly evolved organism such as ours ensures that order will be maintained in its tissues. To achieve metastasis, cancer cells must therefore evade multiple rules and barriers that have been refined over hundreds of millions of years of evolution of the organism. Thus, metastasis is akin to an evolutionary process that involves selection of genetically heterogeneous cancer cell lineages emerging within the highly evolved ecosystem of an organism.

Several steps are discernable in the biological cascade of metastasis. Loss of cellular adhesion, increased motility and invasiveness, entry into the circulation, exit into new tissue, and eventual colonization of a distant site, are essential components of metastatic progression. Seminal work by Isaiah J. Fidler in the 1970s using experimental metastasis assays demonstrated that rare clones within malignant cell populations were endowed with several of these metastasis-promoting functions. The implication was that cells comprising a metastatic lesion were descendants of a rare disseminated cell from the primary tumor that manages to acquire many, if not all, of the genes necessary for successful execution of the metastatic cascade.

Recent technological advances allow validation of these concepts through the analysis of clinical samples. Molecular profiling of cancer using genomic-level approaches has enhanced our understanding of

primary tumors that form metastases. Microarray analyses have highlighted genes whose expression in primary tumors correlates strongly with the likelihood of eventual metastatic recurrence. A recent product of this work has been the identification of specific alterations that allow tumor cells to form metastasis in particular organs, such as metastasis of breast cancer to the bones and lungs. These observations have also prompted a reconsideration of how, when and where cancer cells acquire genes that cause metastasis, and how the activity of these genes could be blocked by new drugs or drug combinations.

On the origin of the species of metastasis

The organ distribution of metastases from a primary tumor is not random. After analyzing secondary cancer outgrowths in a series of autopsies for breast cancer victims, Paget in 1889 proposed that disseminated cancer cells, or «seeds», would only colonize organ microenvironments, or «soils», that were compatible with their growth. Clinical observation of cancer patients supports the notion that circulatory patterns alone, which Ewing in the 1920s was so fond of, provide only a partial explanation for preferred sites of metastasis. For example, systemic breast cancer frequently metastasizes to the lungs, bones, liver, and brain—none of which have a direct circulatory connection to breast tissue. Advanced prostate cancer has a more selective pattern of metastatic recurrence, with bone being the predominant site while visceral organs such as the lungs or liver are much more rarely involved. Uveal melanomas metastasize with astonishing specificity to the liver, and sarcomas to the lungs.

What are the molecular and cellular determinants of unique metastatic tropisms? Recent advances have brought us closer to understanding the molecular and cellular bases for this important aspect of metastasis.

It is now appreciated that at least two classes of determinants affect site-specific metastatic outgrowth. First, there must be an initiation of a viable pre-metastatic niche within the target organ—one that facilitates the initial survival of extravasated tumor cells in a non-receptive target organ. Subsequently, the invading metastatic cell must display the appropriate functions to effectively colonize the new site. Reasoning that different tissues such as the bone marrow, the lung and the brain are of very different structural and cellular composition, one may envision that these tissues present very different selective pressures against cancer cells wandering in from a distant breast tumor. Taking this reasoning to its next logical extension, cells from a given tumor that form metastasis in different organs must represent different metastatic species. Each metastatic species must have the attributes necessary to survive and thrive in its corresponding environment: the bone, the lung or the brain.

Different conditions in different Galápagos Islands selected for different species of finches, as Darwin acutely noticed. A similar process may select for different species of metastasis in different tissues. If we accept the above reasoning, we could further imagine an occurrence with practical applications. In a cancer patient suffering from advanced disease, we could envision the presence in different organs of abundant metastases that are constantly releasing tumors cells into the circulation. These cells would then congregate not only in the bloodstream but also in the fluid of the pleural space that surrounds the lung. In fact, large accumulation of pleural fluid is a typical complication of advanced-stage breast cancer. This accumulation causes extreme discomfort to the patient, and must be drained. The drained fluid is normally discarded as medical refuse but it could be used as a source of metastatic cells. By our logic, these cells would be a mix of the different organ-specific metastatic species present in the patient. Using laboratory techniques, separation of these cells into those that are metastatic to the bones, the lungs or the brain would provide starting material to discover

the genes and functions that allow these cells to colonize different organs.

Experiments like this are in fact being conducted, with success. By isolating and comparing different metastatic cells from the same patients, we can discern the identity of genes and functions that mediate metastasis to specific organs. And, because these genes are mediators of metastasis, they are also potential targets for pharmacological blockers. New drugs could be developed against these genes or their products. Of even more immediate benefit, existing drugs could find new indications by being used in combinations that only now are becoming apparent as a result of this type of research.

The future of the fight against cancer

Our enthusiasm in chronicling these recent advances in cancer research should not distract us from the fact that the clinical impact of these developments is still quite modest. In fact, we owe much of the recent progress in clinical oncology to a more sophisticated use of classical chemotherapeutic drugs and to refinements in surgery, radiotherapy and imaging technologies. Harnessing of the immune system against cancer is enjoying a rebirth with new vaccines to prevent viral infections that predispose to cancer: vaccines against papilloma virus to prevent cervical cancer, and against hepatitis B virus to prevent liver cancer. Anti-tobacco campaigns are reducing the incidence of lung cancer, and mammography and colonoscopy allow the early detection and easier treatment of breast and colon cancers. These methods will remain major means for the prevention and control of cancer for years to come.

Where are we in our quest to understand the genetic and biological basis of all cancer? I would say that in three decades of modern

oncological research we have probably learned 20% of what we need to know. Now, this does not mean that we need another twelve decades for the rest! We should probably be done in another three decades, because the acquisition of knowledge is an accelerating process. And, when are we going to have a satisfactory control over all major types of cancer? This question is more difficult to answer. If by "controlling" cancer we mean reducing it to the same level of control as we now have infectious diseases in industrialized countries, then the goal is well within our reach by mid-century. However, like most infectious diseases, cancer cannot be avoided, let alone eradicated. Cancer is a by-product of life, and the longer we live, the more cancer our organisms will tend to accumulate. Catalonia and Spain as a whole are faced with the same demographic realities as the rest of the industrialized world. Longer life expectancy means a higher overall occurrence of cancer *per capita*.

In light of these realities, it is in the best national interest to equip our society to deal better with cancer. Cancer research has now reached a point at which meaningful advances increasingly result from close teamwork between clinical experts and laboratory scientists. Isolated from each other, as they still are in many of our top research institutions, these two groups of investigators are underpowered to capture the opportunities of modern oncological research. A new culture of integrated research needs to be developed in order to reach a level of proficiency that can in turn generate real fruitful interactions between the academic and industrial sectors.

The chronic limitations in research resources and management leadership of our country have recently undergone meritorious improvements. But these improvements must continue towards publicly stated goals in order to eventually reap the dividends of the investment made. A sustained guidance of the national effort in research and innovation is vital for many nascent sectors. Development of the pharmaceutical industry and public access to optimal cancer

care are but two of the current expectations of our society that depend on robust leadership. Yet, the government's own leadership in scientific research has been intermittent and subject to the vagaries of the political process. To really encourage scientific development and innovation, the scientific leadership needs to be placed on a platform that can withstand changes in political administrations. A strengthening of this leadership and the research resources that go with it remain important national needs that we have inherited from the previous century.

In sum, with the turn of the millennium, cancer research has entered an era that was only a dream in the 1970s, a promise in the 1980s, and a vague reality in the 1990s. This new era is already bringing tangible benefits to clinical practice and a flurry of new activity in the pharmaceutical industry. An optimal convergence of academic research, industrial development, and cancer care delivery system is now possible, and it is something that our society has the right to aspire to.