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A Look Back at more than a Century of Progress in Oncology from the Tumor Cell to the Tumor Environment

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Introduction

During the first half of the 20th century, after the rediscovery of Mendel's laws in 1900, there was a growing interest in determining how these laws of genetics applied, among other things, to mammalian inheritance. In 1909 Morgan's decisive genetic work on the fruit fly, Drosophila melanogaster, with which his name would always be associated, began. Thus, from the beginning of the 20th century, even before the establishment of fundamental knowledge of cell and tissue biology, daring experimentalists sought to explore the nature of tumor tissue by performing intra- and interspecific tumor grafts. The generally very narrow specificity of a tumor for the organism on which it appeared was discussed as early as 1908 by Tyzzer in terms of Mendelian genetics [1]. Later, the genetic theory of tumor transplantability was formulated by Little and Srong [2] in 1924 in the following terms: "The fate of a tumor implanted in a given host is related to the reactions of that host. These reactions are determined to a large extent by its genetic make-up and by those of the transplanted tumor cells, controlled, to a certain extent, by their own genome." In 1937, while studying graft rejection, Peter Gorer [3-6] discovered the H-2 antigen in mice, and thus, unknowingly, he discovered the first major histocompatibility complex antigen, or MHC. (Major Histocompatibility Complex). He was passionate about genetics and his ambition was to identify the genetic causes of cancer. But his greatest contribution to cancer research was the discovery of an important non-genetic cause of cancer (murine breast tumor virus, MTV or Bittner's virus). For 15 years, beginning in 1929, he served as executive director of the American Cancer Society. It is therefore by looking for antigens specific to tumor rejection (characterizing the tumor) that a major element of tissue compatibility and organ transplantation was described.

A transplanted tumor is recognized and rejected as "non-self," through the same process that rejects a normal organ transplant. In addition to this work on tumor transplantation, the authors gradually became interested in the transplantation of normal tissues; Medawar (1944) first reported the use of skin grafts in rabbits. The results obtained allowed Loeb in 1945 to suggest that the transplantation of normal or tumor tissues was dependent on the same fundamental laws. There was no transplantation system specific to the cancer process. During the second half of the twentieth century, relentless and

decisive advances were made in cell biology and molecular biology. It is the understanding of normal cellular mechanisms that has gradually made it possible to identify the abnormal mechanisms involved in cancer pathology. We can take a look at the achievements of the Nobel Prize in Medicine since the 1950s to see that they have accompanied and supported progress in biology and basic oncology.

Developments in Cell Biology

Initially, there were important contributions to "normal" cell biology with the description of the main metabolic cycles ensuring the energy production of the cell and mainly the description of the Krebs cycle. (Nobel Prize in 1953). At the same time, tissue culture systems have been developed that allow experimental models, in vitro, on animal and human tissues. (e.g., permanent cell lines established in ex vivo culture). Developments in genetics initially focused on bacterial or viral DNA, which represented a simplified mode of operation of the genome.

1. Joshua Lederberg was awarded the Nobel Prize in 1958 for his discoveries concerning genetic recombination and the organization of the genetic material of bacteria.
2. Arthur Kornberg in 1959 for the discovery of the mechanisms of biological synthesis of ribonucleic acids (RNA) and deoxyribonucleic acids (DNA).
3. In 1962 Francis Crick, Maurice Wilkins, James Watson, for their discoveries on the molecular structure of nucleic acids and their significance for the transmission of information to living matter.
4. Then in 1965 François Jacob, André Lwoff, Jacques Monod for their discoveries concerning the genetic control of enzymatic and viral syntheses.
5. Peyton Rous in 1966 for his discovery of virus-induced tumors in animals.
6. In 1968 Marshall Nirenberg for the interpretation of the genetic code and its functions in protein synthesis.
7. In 1969 Max Delbrück, considered one of the founders of molecular biology, received the prize together with Salvador Luria for their discoveries concerning the mechanism of replication and the genetic structure of viruses.

The Advent of Immunology and Immunogenetics

Then in the 70s and 80s Important contributions to tissue differentiation and histocompatibility, i.e. tolerance to transplantation, have emerged with the description of the HLA system, which earned the team of Frenchman Jean Dausset the Nobel Prize in 1980. In the 1980s, immunology also became one of the models of immunogenetics with the study of gamma globulins. This study of the conformation and structure of antibodies has been rewarded by the awarding of several Nobel Prizes in the decade on this one subject and this one class of proteins. (Baruj Benacerraf, George Snell, Niels Jerne, Georges J.F. Köhler, Emperor Milstein, Susumu Tonegawa). All this work, after the major contribution of the school of the Pasteurian Jacques Oudin, has made it possible to establish that living species are defined by protein or glycoprotein motifs identifiable on all signaling systems and pathways. These are antigenic motifs present on complex molecules such as antibodies but also on enzymes. Some of these patterns are species-specific, they are recognizable by antibodies developed by other species, these are isotypes. But some patterns localized to other parts of the molecular pattern can vary within a species for each individual, which helped define allotypy. Each individual has, at a given genetic level, a gene from his father and one from his mother. These two genes may be slightly different and represent what are called alleles. These genes perform the same function but represent genetic and functional variation within the species. In their lives, individuals also realize particular phenotypic patterns, they are acquired by a rearrangement, by a new genetic arrangement. This type of rearrangement allows the synthesis of the part of the antibodies that recognizes the antigen. Each individual, including his or her own identical twin, develops different idiotypic patterns to recognize an antigen. These links between genetic regulation and molecular effectors are at the root of one of the fundamental advances in modern cell and molecular biology.

Knowledge of physiological molecular biology will be the basis for comparative studies with cancer cell biology. This is very important because for a long time we have been looking for particular genes, specific to the cancer process, whereas the cancer process is mainly and most often the result of a dysfunction of normal genes. Michael Bishop and Harold Varmus were awarded the Nobel Prize in 1989 for their discovery of the cellular origin of retroviral oncogenes and their relationship to normal cellular genes. Another fundamental discovery of the early 1970s [7], attributed to Peter Doherty and Rolf Zinkernagel, (1998 Nobel Prize), is the restriction function attributed to the major histocompatibility complex (MHC) of T cells (natural killers of tumor cells). It has led to a better understanding of antigen recognition by T cells. This breakthrough also led to other major discoveries on the ontogeny and immunobiology of T cells and catalyzed a renaissance of viral immunology with extensions on anti-tumor immunity and immune tolerance.

Oncogenes

A very important advance was made at this point in the 1980s, with the description of cancer genes (oncogenes) exerting a dominant effect on the cell and cancer genes exerting a recessive or suppressor-like effect. This means that in order to undergo a stage of carcinogenesis, it is sufficient for the tumor to be subjected to the effect of a dominant oncogene (one of the two genes located at the same genetic level), whereas the tumor must lose the function of two normal allelic suppressor genes or keep only one but inactive. (Recessive oncogene).

New Paradigms About Carcinogenesis

It is also important to note that there has been a shift in the paradigm around carcinogenesis. For a long time, work focused on the abnormalities gradually accumulated by normal cells to acquire functional independence and unlimited multiplication. This progression and distancing towards the cancerous phenotype by cellular abnormalities accumulated step by step, is a peculiarity of solid tumors. The complexity of solid tumors is much greater than that of hematological models, especially leukemias. In the latter models, a small number of gene-specific events contribute to the establishment of a cell line characterizing a hematologic malignancie.

The Tumor and Its Environment

For solid tumors, the paradigm of considering the tumor and its environment as a whole has gradually emerged. This set has traits specific to tumor cells and traits specific to the tumor environment that can promote or control tumor development. Today, it is this concept that combines the description of tumor abnormalities with those of the functional profile of the environment that represents the true identity of a tumor process. This observation is all the more important since the signalling used to identify, tolerate or reject a tumor is based on very specific signals for which pharmacological interventions can now be proposed, particularly with monoclonal antibodies. So-called "monoclonal" antibodies are antibodies initially made by cultured plamocyte cells, but synthetic repertoires and transgenic animals are also used to produce them. Several hundred monoclonal antibodies are currently marketed for the treatment of chronic inflammatory diseases and especially autoimmune diseases, and of course for the treatment of cancers and transplant rejection. They have revolutionized the management of many diseases.

A New Tumor Geography Illustrated: Immunohistochemistry (IHC)

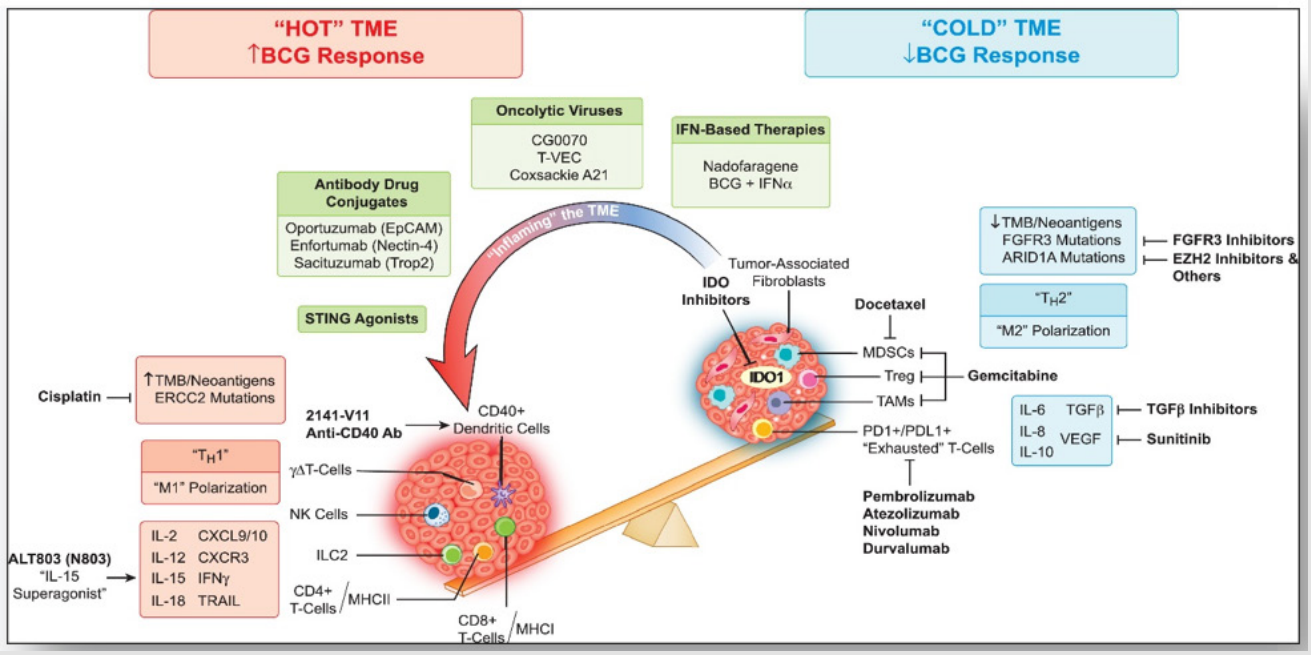
The topographic picture of the relationships between tumor cells and non-tumor cells can now be revealed in immunohistochemistry and in particular enhanced by multiplexed immunohistochemistry techniques, where all the protagonists of a tumor development system can be revealed simultaneously on the same histological section. It is therefore the interest to develop the mastery of this technique in the context of a cancer pathology activity, because all tumors will be treated in the short term according to personalized criteria defining a tumor identity, which will be the indication for a highly specific targeted treatment.

The Nobel Prizes that have marked this evolution are:

1. R. Timothy Hunt and Paul M. Nurse in 2001 for their discovery of cyclin and cyclin-dependent protein kinases, fundamental molecules for cycle regulation and cell multiplication.
2. Sydney Brenner, H. Robert Horvitz, John E. Sulston in 2002 for their discoveries concerning the genetic regulation of organ development and programmed cell death. (P. Death)
3. The identification of the first cancer-causing virus in humans earned Harald zur Hausen the Nobel Prize in 2008 for the genetic identification of human papillomaviruses (HPV 16 and 18) responsible for cervical cancer.
4. James P. Allison and Tasuku Honjo were awarded the Nobel Prize in 2018 for their discoveries in immunotherapy. These discoveries have made it possible to take a decisive step forward in the knowledge of cancer treatment.

The models or paradigms of oncology have therefore evolved with the attention paid to tumor cells to gradually extend to the tumor environment. More recently, for solid tumors, this tumor environment has been considered for its tumor defense or tumor tolerance capabilities. The aim is to recognize a new system of balance between the characteristics specific to the tumor, i.e. the potential antigenic targets carried by the tumor, the immune skills of the host and the action of all the cell categories present (Figure 6). Fibroblasts make up the most abundant connective cell population in the stroma. In the context of epithelial tumors, many of them are in an activated state with a characteristic of "carcinoma-associated fibroblasts" (FAC). Detection of FACs is generally associated with an unfavorable clinical prognosis, as these cells play a major role in each stage of tumorigenesis, whether during tumor initiation, growth, invasion, or metastatic development.

During tumor progression, many interactions are established between cancer cells, the surrounding tissue, and the extracellular matrix. Tumor cells can thus alter their microenvironment by making it permissive and conducive to their growth; In turn, the tumor microenvironment contributes to or enables the migration of these cells and, as a result, distant tumor invasion. Such cooperation plays a fundamental role in the evolution and metastatic development of the tumor. It is the evaluation of this set of immunocompetent cells, inflammatory cells and activated non-tumor connective or vascular cells, associated with the tumor, that justifies an integrated approach to these parameters. These different populations of the tumor microenvironment work synergistically to achieve a tumor-hostile "hot" environment or a permissive "cold" environment. Figure 1 shows the various therapeutic agents known to tip this environment towards tumor regression.



Note: TME, tumor microenvironment; BCG, Bacillus Calmette-Guérin; TMB, tumor mutational burden; FGFR3, fibroblast growth factor 3; IL, interleukin; IFN, interferon; IDO, indoleamine dioxygenase; TGF, transforming growth factor; NMIBC, non–muscle invasive bladder cancer; NK, natural killer; PD-1/PD-L1, programmed cell death-ligand 1; MDSC, myeloid-derived suppressor cells; VEGF, vascular endothelial growth factor.

Figure 1: Therapeutic strategies that induce a conversion of a cold tumor microenvironment to a warm environment in non-invasive bladder cancer (NMIBC).

Immnohistochemistry: Phenotypic Loss, Phenotypic Gain, Phenotype-Genotype Links

In paraffin-fixed and paraffin-embedded tumor tissues, antigens can be accessed that have been restored by biological and/or physical processes. Access to these different patterns, present in tumors or in normal tissue, represents a real revolution, especially as it allows for increasingly legible and explicit images. Tumor tissues that have been embedded for a long time can also be used retrospectively (Figure 2 and 4). These images can be seen as a battlefield with combatants that are illustrated by different colored signals (Figure 6) Carissa Chu MD, Eugene Pietzak MD. Figure 1 D'après "Immune mechanisms and molecular therapeutic strategies to enhance immunotherapy in non–muscle invasive bladder cancer: (NMIBC). Invited review for special issue "Seminar: Treatment Advances and Molecular Biology Insights in Urothelial Carcinoma". Available online 8 July 2022.

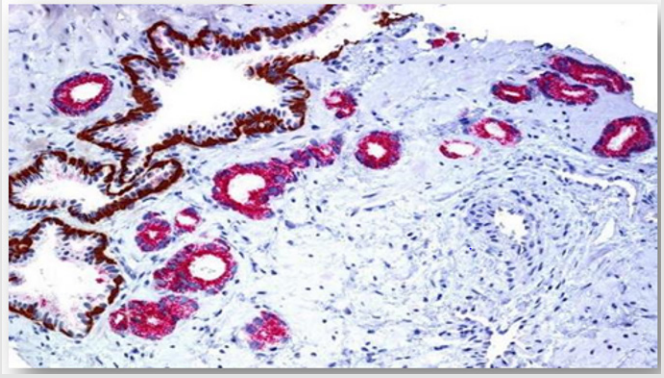


Figure 2: Immunohistochemistry includes phenotypic loss and phenotypic gain. The tumor cells in the example above have lost their basal boundary which is normally colored brown. In addition, they have acquired an enzymatic activity that is not present in normal cells, racemase, which is stained red (UNILABS Lausanne CYPA).

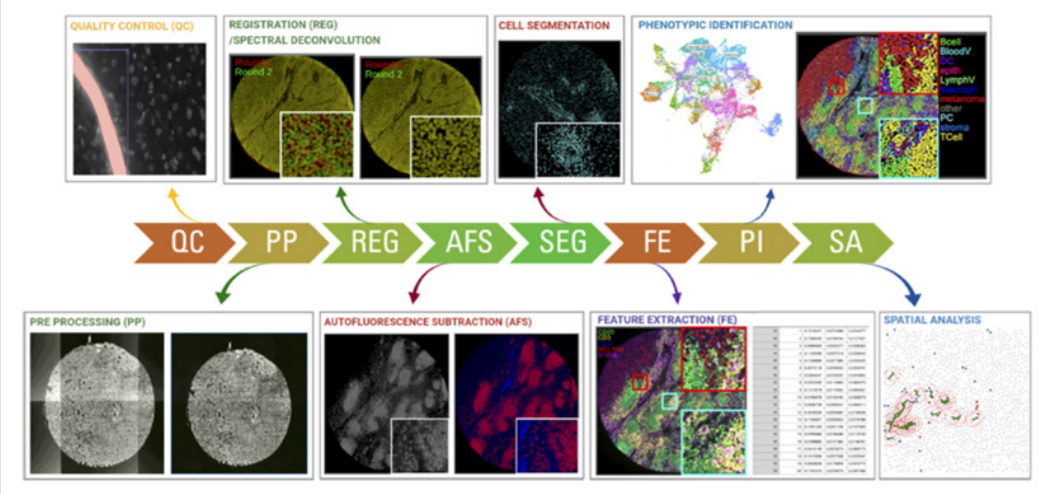


Figure 3: Schematic overview of the steps required for image analysis using the most commonly used fluorescent methods for multiplexed IHC. The images are collected over several cycles and must undergo quality control (QC) as well as initial processing (PP), registration for spectral deconvolution (REG), correction by subtraction of autofluorescence (AF), cell segmentation (SEG), extraction of cell characterization elements (FE) for phenotypic identification (PI) and finally, spatial distribution analysis (SA) According to Frontiers in Oncology | https://www.frontiersin.org/ July 1, 2022 | Volume 12 | Article 918900 Next-Generation Pathology Using Multiplexed Immunohistochemistry..

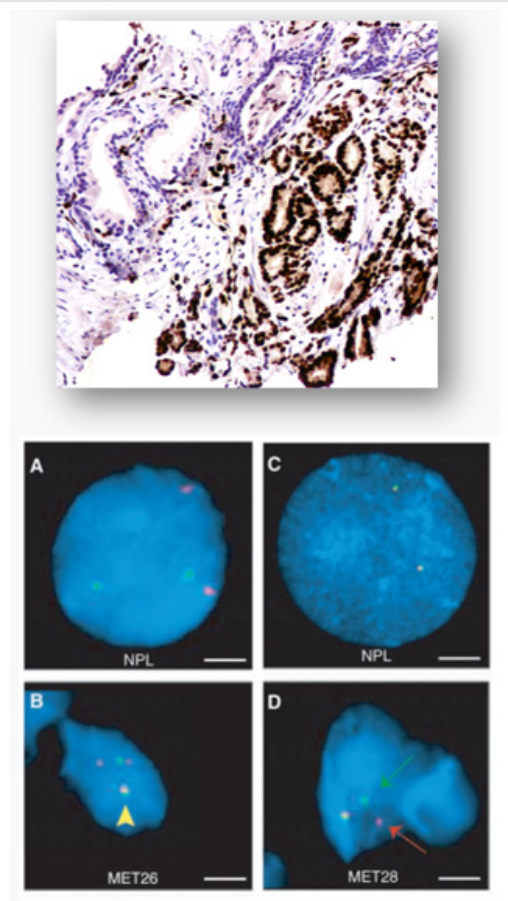


Figure 4: Genotype-related immunohistochemical phenotype. Figure 3A top: Nuclear expression in IHC of the fusion protein Erg/TPMRSS2. Figure 3B bottom: in situ hybridization showing the fusion of the two genes in B. Transcription Factor Genes in Prostate Cancer Recurrent Fusion of TMPRSS2 and ETS Science 310, 644 (2005); Scott A Tomlins, et al.

Cancer Immunoediting

Cancer immunoediting is the process by which the immune system controls tumor development and shapes tumor immunogenicity, it comprises three phases: elimination, equilibrium, and escape [8-14]. Although many of the immune components involved in this process are known, the underlying mechanisms remain poorly defined. A central tenet of cancer immunoediting is that T cell recognition of tumor antigens leads to the immunological destruction or sculpting of a cancer. However, much of our current understanding of tumor antigens comes from analyses of cancers that develop in immunocompetent hosts and may therefore have already been "edited." Little is known about the antigens expressed in nascent tumour cells. Are they sufficient to induce protective anti-tumor immune responses or is their expression modulated by the immune system?. Using massive parallel sequencing, such as NGS, some authors were able to characterize mutations expressed in highly immunogenic methylcholanthrene-induced sarcomas derived from immunodeficient Rag 2 mice. The cells of these sarcomas phenotypically resemble native primary tumor cells [11,13].

It has also been considered with this type of model that cancer immunoediting occurs via a T-cell-dependent immunoselection process. This selective process promotes the growth of clones of pre-existing tumor cells lacking mutant β-spectrin-β2, lacking the HLA system and the different components of tissue phenotypic identity. There would therefore be a loss of the registers of restriction, i.e. of tumor identity linked to the HLA system, with a consequent loss of recognition of cellular targets. This work tends to prove that the high immunogenicity of an unedited tumor can be attributed to the expression of highly antigenic mutant proteins and suggests that the development of tumor cells lacking these potent antigens is promoted via a T-cell-dependent immunoselection process. This antigenic silence represents a likely mechanism of cancer immunoediting. In the human clinic, evidence of immunoediting in patients is very complex to obtain and remains the subject of many questions, especially when treatments have already been applied.

Danger Signals Emitted by Cell Damage

Protective immunity against pathogens is usually invoked by the detection of highly conserved microbial structures, structures called pathogen-associated molecular patterns (PAMPs). Over the past few decades, studies [14] have revealed how the immune system recognizes damage to uninfectedtissue [15]. Molecules released by necrotic cells or secreted by immune cells during tissue stress, called molecular damage-associated models (DAMPs), have been postulated as homologous to PAMPs. These PAMPs and DAMPs are defined as exogenous and endogenous "danger signals"[16]. They can not only be instrumental in inducing the response, but also potentially guide the type of immune response needed to help hosts defend themselves against aggressive pathogens. This response, by eliminating antigens or repairing damage, will promote cell growth in order to restore tissue homeostasis after injury.

This type of response (to PAMP, DAMP) is largely mediated by innate immunity, whereas the example illustrates adaptive immunity. Innate immunity plays a crucial role in immunoediting by introducing tumor antigens to T cells. This is of great importance because combinatorial therapy (which is part of precision oncology) combines therapeutic approaches that target the tumor compartment and the innate immune compartments (e.g., anti- CD47 (Figure 5)) and adaptive (e.g., anti-PD-1 (Figure 6)). Combinatorial therapy illustrates the major need for multiplexed detection. Combinatorial therapy is particularly relevant to phase I clinical trials.We will see below what the therapeutic prospects are in this regard, see "Bacteria-Based Cancer Immunotherapy [15]".A growing body of evidence suggests that many tumors naturally induce antigen-specific adaptive immune responses [17]. However, it is still unclear precisely how the immune system recognizes a growing tumor, especially for tumors that originate from a sterile organ, devoid of any exogenous danger signals derived from microbial signals. But the hazard signals are now recognized as related to tumor immunogenicity. Although cancers damage tissues and are considered "wounds that do not heal" [18], it is not understood whether DAMPs play a role as a "danger signal" to induce a spontaneous immune response during tumour progression and whether these reactions can produce an abscopal effect, also known as an effect of radiotherapy. D'après cancer Res. 2013 Jan 15; 73 (2):629-639. Tissue damage-associated "danger signals" influence T-cell responses that promote the progression of preneoplasia to cancer.

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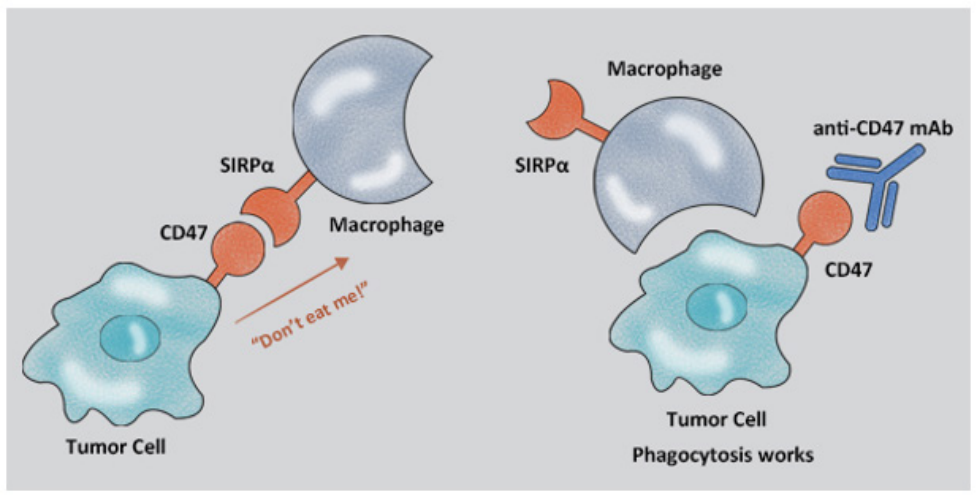

Figure 5: Pattern of action of therapeutic antibodies targeting CD47. The antibodies block the interaction between CD47 and its Sirp-alpha ligand, inhibit the "don't eat me" signal, and restore phagocytosis of tumor cells by macrophages.

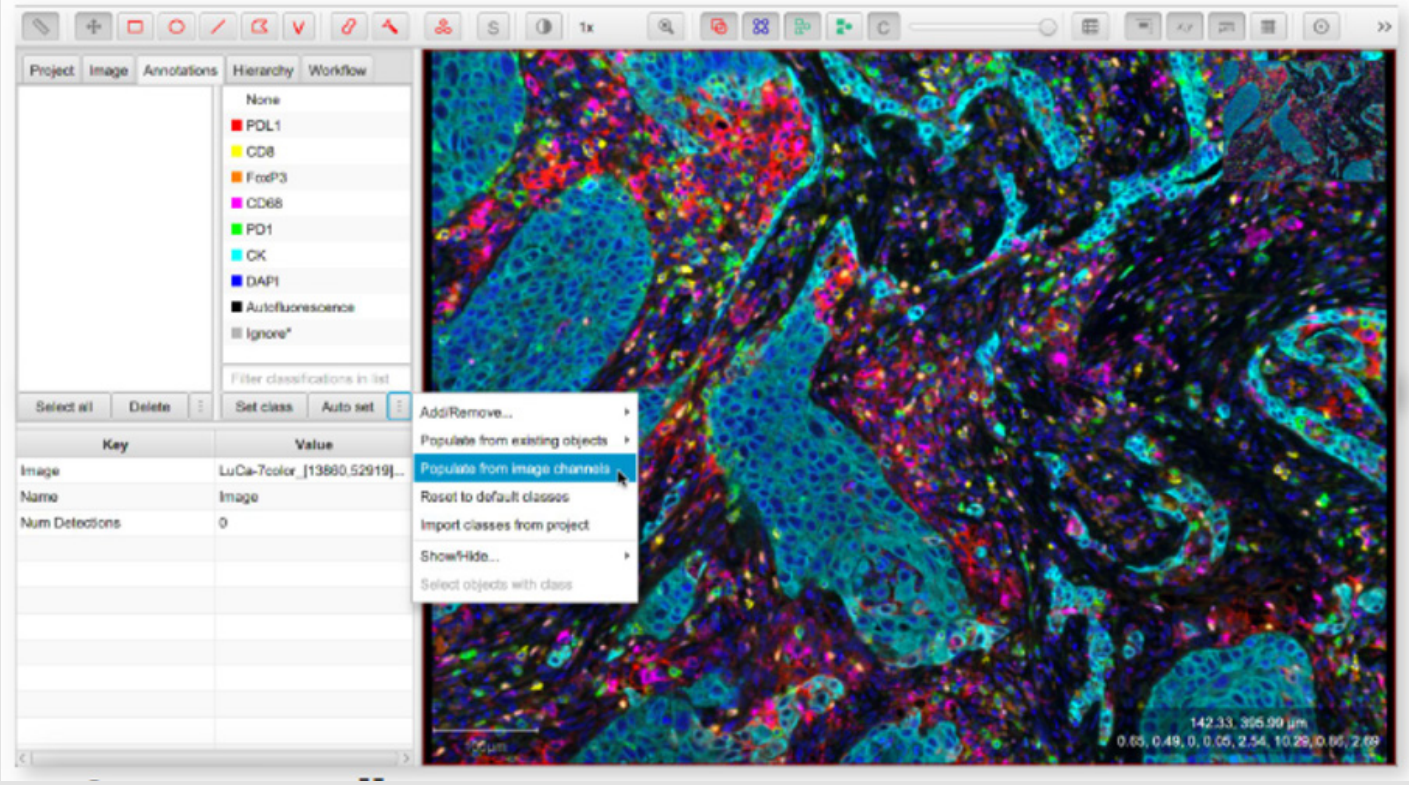

Figure 6: Image from a tutorial (Q path). Multiplexed detection with evidence of the tumor environment. The tumor is blue. Immune cells in other colors. Expression of PD-1 and its ligand PD-L1 is visible in the tumor and stromal compartment.

The Age of Agnostic Treatments

For many years, drugs to treat cancer have been tested and approved in the United States by the Food and Drug Administration (FDA) based on the histological type and anatomical location of a tumor tissue. For example, a drug was approved to treat breast cancer, prostate cancer, or lung cancer (or sometimes more than one type of cancer).Over the past two decades, much has been learned about specific changes in genes and proteins in cells. The aim was to identify what causes them to grow uncontrollably and become cancer cells. (These genetic and protein modifications are also called biomarkers.) The discovery of these specific changes in cancer cells is unique to a person, which should decide their personalized treatment. For example, in people with lung cancer, or lymphoma, cancer cells are now tested for genetic (Figure 7) or protein (phenotypic Figure 8) changes to determine whether certain targeted drugs might be effective.

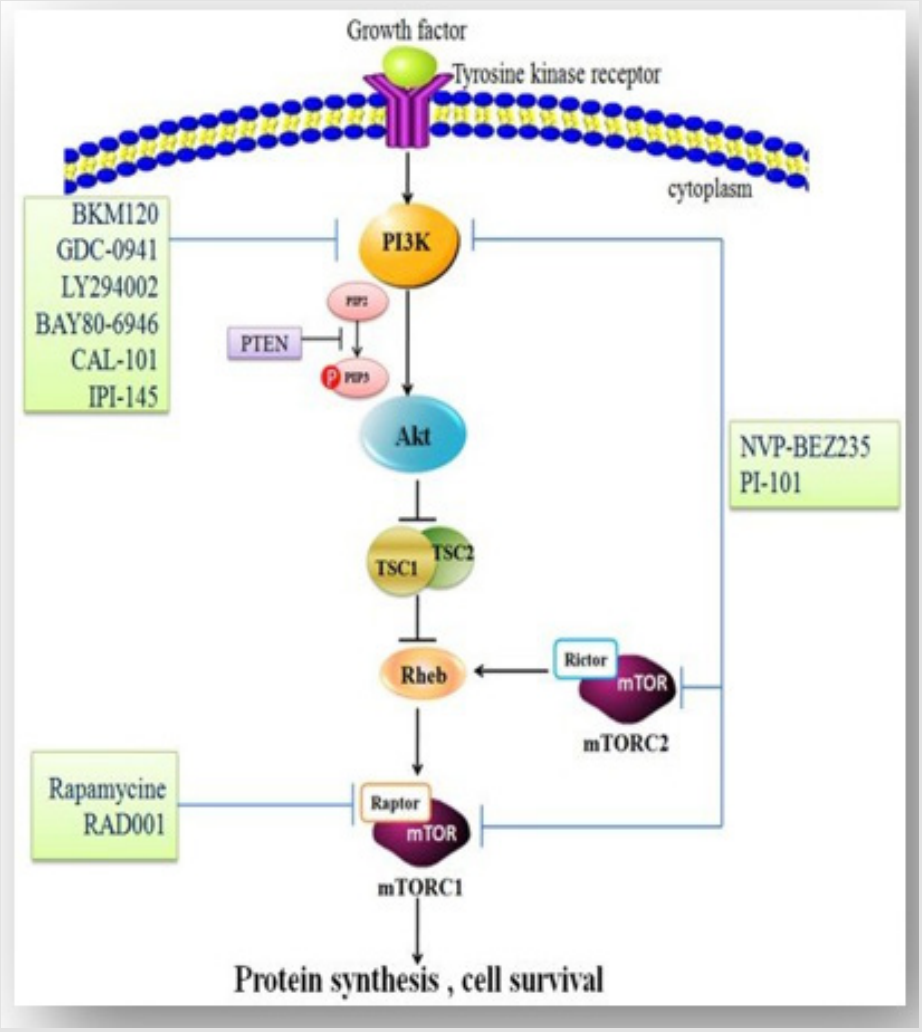

Figure 7: The PI3K/Akt/mTOR pathway and its inhibitors in lymphoma. Once tyrosine kinase receptors are bound to growth factors, the PI3K signaling pathway is activated to lead to cell survival which conditions the increase in tumor population.

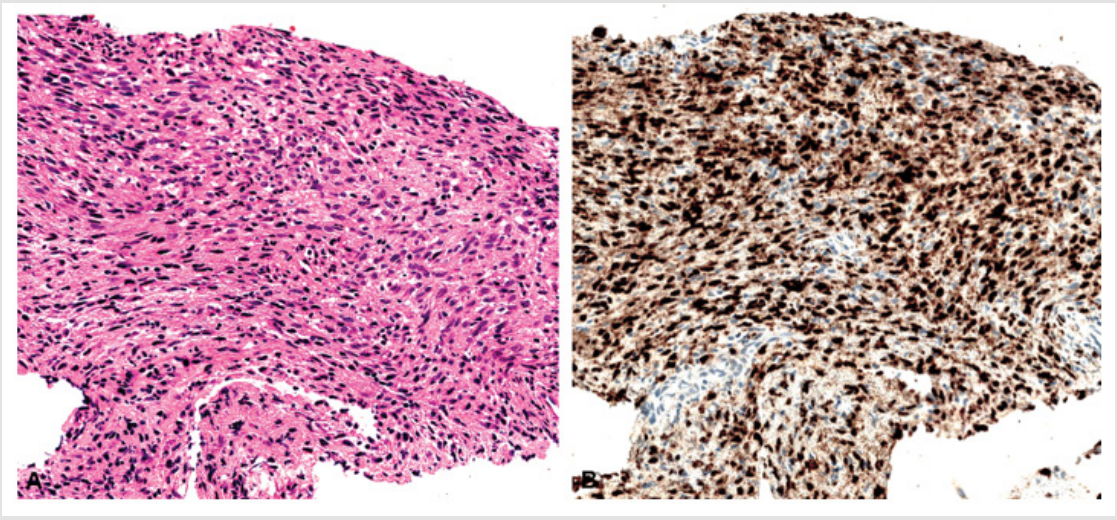

Figure 8: Example of identification of tumors related to a gene fusion of the NTRK type. Infantile fibrosarcoma with ETV6-NTRK3 fusion (Oncomine Comprehensive Assay v3, Thermo Fisher Scientifics). Left-hand panel, histology. The tumor is formed by bundles of ovoid and spindle-shaped cells with moderate cellular atypia. Right panel: Pan-TRK immunohistochemistry shows diffuse and strong nuclear staining associated with lower cytoplasmic granular positivity (Ventana Medical Systems, Tucson, Arizona) (hematoxylin-eosin, original magnification ×200 [A]; original magnification ×200 [B]).

To take it a step further, some drugs are now approved primarily based on whether the cancer cells have specific genetic or protein changes, regardless of the organ or tissue where the cancer started. Drugs approved for use on this principle are called agnostic drugs. Immunotherapy and targeted therapy are new treatments that are changing the way oncologists treat a tumor based on its specific genetic profile rather than its anatomical location or tissue of origin. There are two examples; Already in 2018, the Food and Drug Administration (FDA) approved Larotrectinib (Vitrakvi), a tropomyosin kinase receptor (NTRK) inhibitor TrkA, TrkB and TrkC, to treat solid tumors expressing very specific genetic characteristics (Figure 8). Another approval is for Pembrolizumab, a humanized monoclonal antibody that binds to the programmed death-1 (PD-1) receptor and blocks its interaction with the PD-L1 and PD-L2 ligands. The PD-1 receptor is involved in the control of T cell immune responses, as it produces a downregulation of the activity of these immune cells present as we have seen in the tumor environment. These two examples illustrate the breakthroughs that have been made in the development of "tumor type-independent," "site-independent," or "histology-independent" drugs. But what exactly does "tumor agnostic character" mean, and why is it important for people with cancer [19] to learn more about these types of treatments that are emerging? Pan-TRK Immunohistochemistry: example of identification of tumors linked to a gene fusion of the NTRK type .As we have seen, much has been learned in recent decades about specific changes in genes and proteins in cell physiology.

These changes allow cells to grow uncontrollably and become hostile cells. (These genetic and protein modifications are recognized as tumor biomarkers.) The identification of these person-specific changes in cellular and molecular pathology makes it possible to choose a treatment. For example, in people with lung cancer, cancer cells have now been tested for several years to identify genetic or protein changes to determine whether certain targeted drugs might benefit them [19]. So some drugs are now approved primarily based on whether the cancer cells have specific genetic or protein changes, regardless of where in the body the cancer started. Drugs approved for use on an agnostic tumor feature are called agnostic drugs.

Bispecific Antibodies

Bispecific antibodies are antibodies designed so that each of their recognition sites can bind to a different antigen. In principle, such molecules can operate in a more specific way by targeting two types of receptors located on the surface of the cells that are to be eliminated. The risks of targeting healthy cells, which are not involved in the therapy, are reduced accordingly. Bispecific antibodies can target antigens belonging to two different cell lines (e.g., a tumor cell and an immune system killer cell). This strategy makes it possible to connect and activate cellular modes of interaction that would not occur naturally.

New Approach: Antibodies Coupled with a Therapeutic Agent

The current standard of care for advanced urothelial carcinoma includes platinum chemotherapy and immunotherapy. Antibody-drug conjugates (ADCs), originally developed for hematologic malignancies, implement potent antibody-bound cytotoxic agents that recognize specific antigens carried by the not tumor; This rational drug design allows for more targeted efficacy, while mitigating systemic toxicity.

Study [21] Reviews Emerging ADC Landscape Regarding Urothelial Carcinoma

Enfortumab vedotin anti-Nectin-4 ADC has demonstrated efficacy in prospective studies in patients with advanced urothelial carcinoma in multiple settings, alone or in combination with pembrolizumab. The anti-Trop-2 ADC sacituzumab govitecan has also shown efficacy in single-arm studies. Both conjugates received prompt and full approval from the Food and Drug Administration. (FDA). Commonly observed adverse events include rash and neuropathy for enfortumab vedotin, myelosuppression, and diarrhea for sacituzumab govitecan. Several human epidermal growth factor receptor 2 (HER2) ADCs are in clinical trials. For localized bladder cancer, an anti-epithelial cell adhesion molecule (ADC) oportuzumab monatox is being studied in patients refractory to intravesical therapy with bacillus Calmette-Guérin (BCG). Antibody-drug conjugates to treat urothelial carcinoma are now approved and emerging as therapies for patients with advanced urothelial carcinoma, filling the previous void for the treatment of progressive disease. Ongoing studies are also evaluating these agents in the neoadjuvant and adjuvant settings.

A Weapon for the Future: Bacteria-Modulated Immunotherapy [20]

Over the past decade, bacteria-modulated cancer immunotherapy has been the focus of much academic research due to its unique mechanism and numerous applications in triggering anti-tumor host immunity. An advantage of bacteria is their ability to target tumors and preferentially colonize the central area of the tumor, which is difficult for other vectors to access. Bacteria are numerous among the molecular patterns associated with pathogens that can effectively activate immune cells, some previously defined as "danger signals." This efficacy can manifest itself in the immunosuppressive microenvironment of the tumor. Bacteria are able to enhance specific immune recognition and the elimination of tumor cells. More interestingly, during the rapid development of synthetic biology, the use of genetic technology has led to creative new paradigms of immunotherapy. These developments should enable bacteria to be effective producers of immunotherapeutic agents. The combination of bacteria and nanomaterials also deploys infinite imagination in the multifunctional endowment for cancer immunotherapy. Important reports 20 summarize recent advances in bacteria-based cancer immunotherapy. They emphasize applications based on naïve bacteria, modified bacteria, and bacterial components. These publications also discuss future directions in this area of research. The precise identification of the tumor microenvironment will play a central role in this scheme and will be a prerequisite for the use of this treatment strategy (Figure 9 and 10).

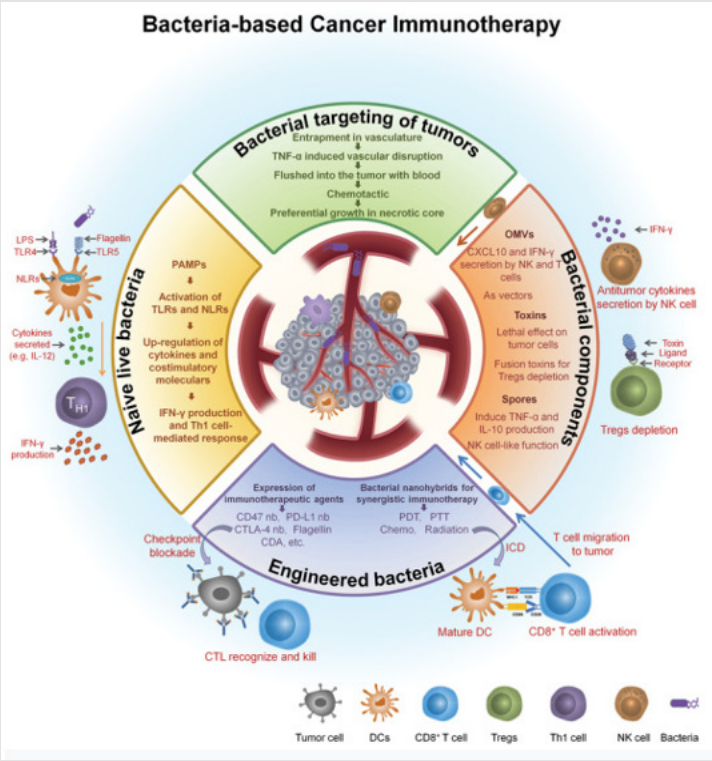

Figure 9: Overview of Bacterial Immunotherapy 14. Mechanism of bacterial targeting of tumors, how naïve live bacteria activate the immune system, different strategies of modified bacteria and their link to immunotherapy, and activation of the immune system by different bacterial components 20.

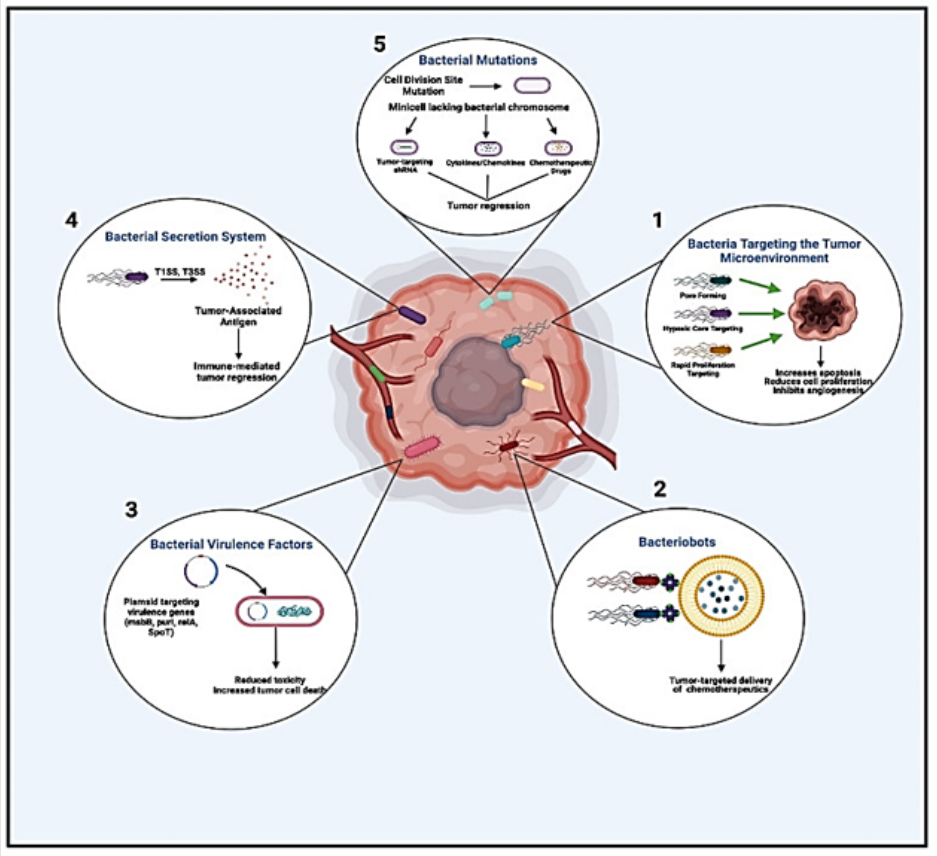

Figure 10: Schematic summary of the different bacterial mechanisms used in bacterial cancer therapy

1. Anaerobic bacteria specifically target the hypoxic environment of tumors by triggering an inflammatory response resulting in tumor destruction.
2. Bacteriobots for cancer treatment, which involve targeting controlled drug delivery, improved cell adhesion, and improved cell penetration.
3. Bacterial virulence factors may be bioengineered to reduce toxicity and increase tumor cell death.
4. Bacterial toxins, such as the bacterial secretory system (T1SS and T3SS), can be used to inhibit the growth of solid tumors.
5. Bacterial mutations facilitate the delivery of immunomodulators such as cytokines, chemokines, and small molecules as well as immune checkpoint antibodies, which can stimulate anti-tumor responses.
6. This figure was created using Biorender.com.

Conclusion

A few points stand out in this race that has been going on for more than a century.

1. After the complete sequencing of the human genome obtained in the 2000s, it was realized that the exhaustive list of gene composition was largely insufficient to understand their regulation.

2. The reading of phenotypic effectors should be considered as the end of execution of a program resulting from a polygenic signaling cascade, a complex chain of receptors and effectors.

3. Tumors in different organs may share common oncogenetic mechanisms. Thus, it is no longer enough to characterize a tumor by the tissue from which it is supposed to originate or to which it resembles. A tumor is agnostic, it must be characterized by the active signaling pathways involved in its transformation, as they may become the target of treatment.

4. The environment of the tumor and its particular complete kinetics must be taken into account, including in the immune status of its environment. There is a reciprocal influence of the tumor cell compartment on the stromal compartment. The influence is exerted at multiple levels: genomics, transcriptomics, epigenetics, proteomics (functional phenotype and signal transduction) and metabolomics.

5. To emphasize the interest of a multiplexed imaging approach, it should be noted that having an image comparable to a

geographical map locating the tissue protagonists (an augmented reality) is a considerable advance (Figures 3 and 6).

6. We now know that the analysis of these images will be subject to artificial intelligence or computerized image analysis tools that will reduce the amount of subjectivity for the quantitative interpretation of the signals. Current tools measure qualitative and quantitative aspects, they measure the expression of targets, their distribution in tumor and stromal cells. They measure the distance between distinct cell types and provide information on cellular dialogue and its alteration by the tumor microenvironment.

7. While these tools are used in research and development, they are not yet frequently used in the clinic. However, the growing success of combinatorial therapy (the only way to effectively understand and combat tumor heterogeneity and complexity) will require the rapid adaptation of these techniques to the diagnosis and treatment of cancer.

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