Hypothesis

Self-Assembling Antisense Oligo-RNA Structures and M2-M1 Macrophage Phenotype Transformers for Cancer Treatment

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Self-Assembling Antisense Oligo-RNA Structures and M2-M1 Macrophage Phenotype Transformers for Cancer Treatment

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Abstract

The effectiveness of modern cancer therapy is significantly limited by rapid tumor adaptation, multiple drug resistance mechanisms, and the formation of an immunosuppressive microenvironment supported by M2 phenotype macrophages and latent viral infections. In this paper, we present an innovative binary therapeutic system designed to overcome these fundamental barriers. The first component of the system, MoLRx (mixture of antisense oligoRNA), is based on technology that converts the entire pool of eukaryotic RNAs from baker's yeast into antisense oligonucleotide structures via chemical modification of nucleotide bases (exo- and endo-cyclic). Due to the hyperactivated macropinocytosis characteristic of most solid tumors, MoLRx selectively penetrates cancer cells and forms stable hydrogen-ion bonds with the entire pool of cellular RNAs (mRNA, tRNA, rRNA). The absence of RNA repair mechanisms makes this multi-target approach resistant to tumor mutational adaptation and effectively blocks protein synthesis. The second component, Lipo-Liasten, is a liposomal penta-muryl peptide that acts on the tumor microenvironment, inducing macrophages to shift from the pro-tumor M2 phenotype to the pro-inflammatory and anti-tumor M1 phenotype. This leads to the reactivation of NK cells and the removal of the immunological block created by T-suppressors. The combined use of MoLRx and Lipo-liasten produces a synergistic effect: inhibiting tumor cell proliferation and restoring systemic antitumor immunity. The proposed strategy allows effective treatment of resistant and metastatic forms of cancer, while avoiding the development of tumor lysis syndrome and typical mechanisms of drug escape.

Keywords: antisense therapy; MoLRx; M2-M1 macrophages; macropinocytosis; immunosuppression; muramyl peptides; targeted delivery

Introduction

1. The problem of treating cancer

In recent decades, several successful new approaches have emerged for the treatment of cancer. In particular, targeted drugs and monoclonal immunoglobulins—immune checkpoint inhibitors [1,2]. These drugs are relatively non-toxic because their action is directed precisely at a specific target (protein) or mechanism. Unfortunately, tumors adapt and evade these promising drugs after only a few courses of treatment [3]. Of course, patients' lives are prolonged, and their quality of life is improved thanks to these promising areas of cancer therapy. But this does not last long. Surviving cancer cells become not only resistant to a specific drug but also to the entire spectrum of existing chemotherapy drugs [4]. First, we need to understand why tumors rapidly adapt to virtually all existing chemotherapies, why metastases, especially distant ones, are largely insensitive to the chemotherapy previously used in a given patient, and why replacing components of

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polychemotherapy has no effect—the tumor does not shrink or die. The only thing that targeted drugs and immune checkpoint inhibitors have achieved is to prolong patients' survival by several years [5,6].

2. General characteristics of tumors that prevent effective chemotherapy for cancer

Solid tumors are essentially additional organs composed of multiple cell types, including cancer cells (in the form of several clones), immune cells, neuroglia (in brain tumors), connective tissue cells, and others [7,8]. We highlight the presence of multiple cancer cell clones within a tumor [9–11]. Clones are groups of cancer cells from different generations that exhibit distinct surface antigen profiles [12]. In addition, some of these clones are dormant, and the cells in them do not divide. One such clone generation is distant metastases [13].

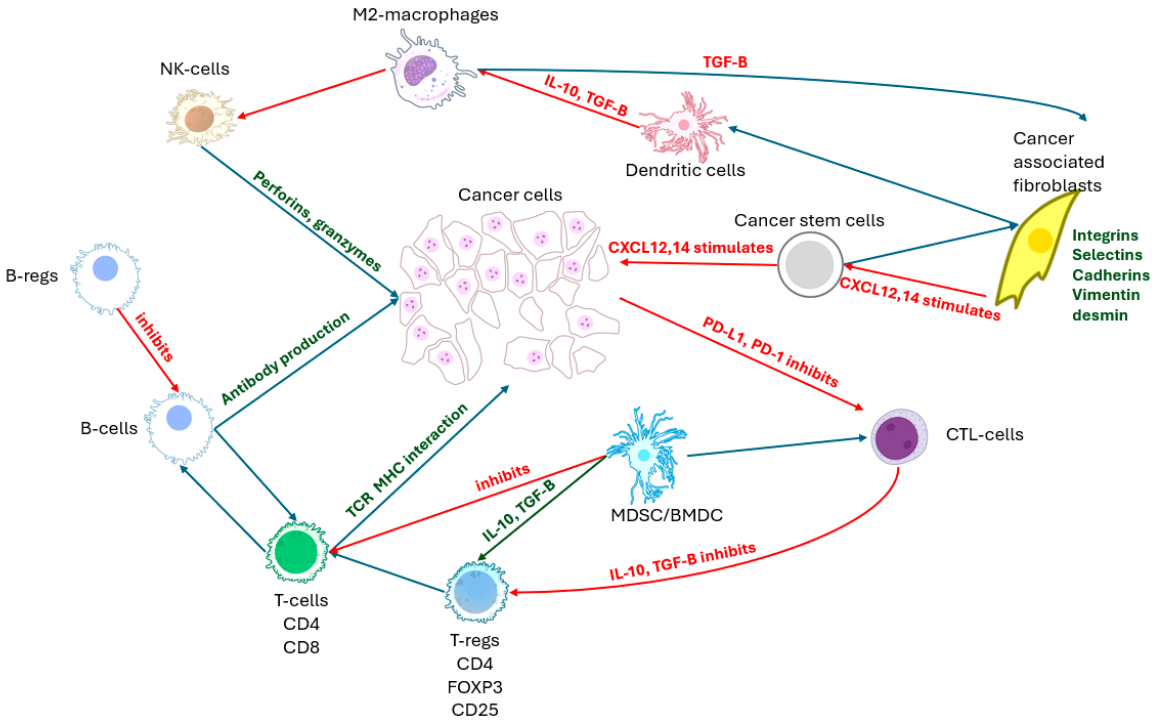

Figure 1. Schematic overview about the most important mechanisms and interactions of the tumor microenvironment (TME) [14].

As long as the central tumor is present and dividing rapidly, the daughter metastatic cells remain dormant and do not grow into tumors [15,16]. The mechanisms by which some clones inhibit others remain incompletely understood. However, there is a well-documented phenomenon in which, following surgical removal of the primary tumor, distant metastases can grow rapidly [17]. It is likely that the parent tumor secretes a set of growth inhibitors for daughter metastases. These facts are directly relevant to the effectiveness of various chemotherapy and radiotherapy methods for cancer. Most classic anticancer drugs act as inhibitors of one or more stages of the cell cycle [18].

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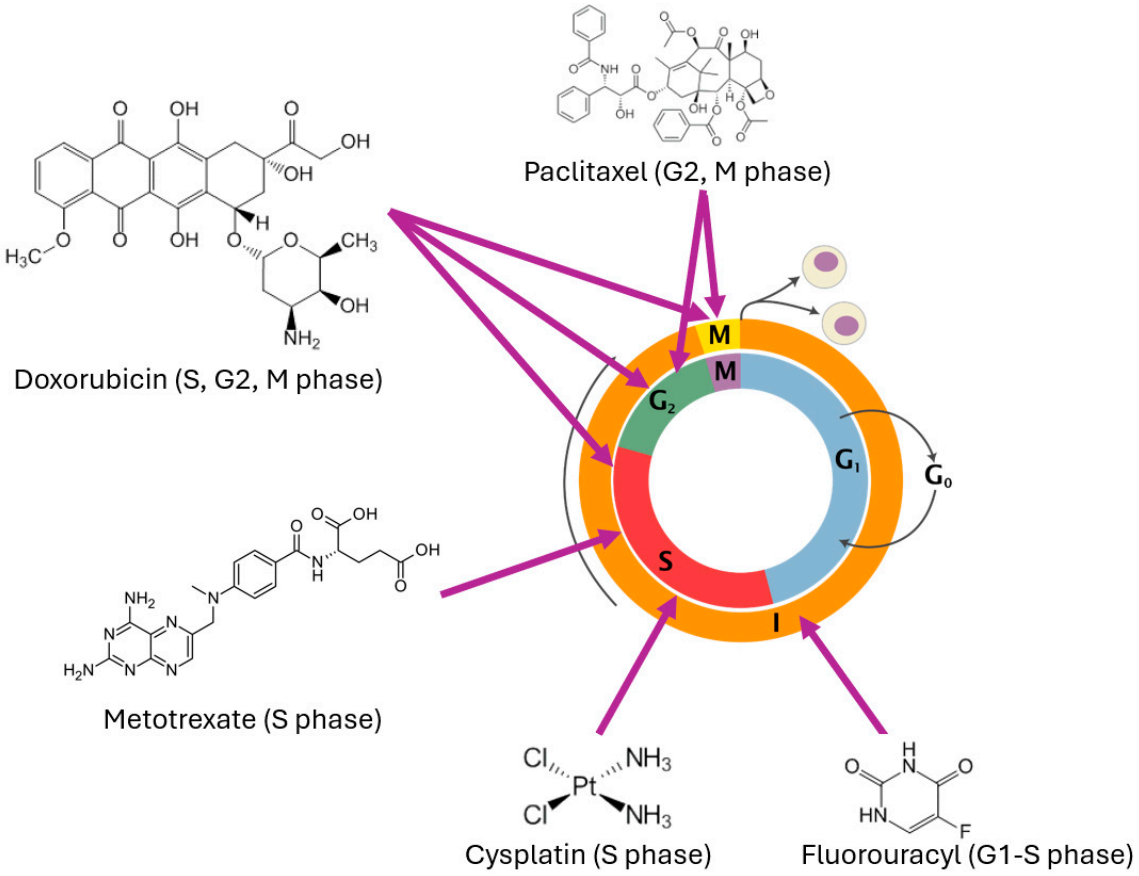

Figure 2. Suppression of the cell cycle of cancer cells by classic anticancer drugs.

Schematic of the cell cycle. Outer ring: I = Interphase, M = Mitosis; inner ring: M = Mitosis, G1 = Gap 1, G2 = Gap 2, S = Synthesis; not in ring: G0 = Gap 0/Resting [19]

Thus, the primary task of classic anticancer drugs is to inhibit cancer cell division and tumor growth [20]. Such drugs are ineffective against dormant cancer cell clones and distant dormant metastases [21]. In addition, such dormant cancer cells trigger a protective mechanism—the expression of P-glycoprotein (a cell membrane "vacuum cleaner")—which removes toxins from the cytoplasm, preventing their entry into deeper cellular compartments [22,23]. In recent decades, this mechanism has been supplemented by the overexpression of DNA repair factors and the rapid phosphorylation of repair system components [24]. These proteins are 1,000 times more active, and their numbers also exceed the norm several-fold in quiescent metastases treated with sublethal doses of chemotherapy, compared with initial metastases and somatic cells. As soon as standard chemotherapy kills dividing, growing cancer cells, only quiescent clones and metastases survive [25]. The growth-inhibiting factors secreted by the central tumor immediately disappear, and the quiescent cells begin to multiply. However, these cells already express the universal P-glycoprotein and overexpress the DNA repair apparatus. In this case, absolutely all anticancer drugs and radiation therapy in any combination become ineffective in the fight against secondary tumors and metastases [26]. Attempts to use P-glycoprotein inhibitors in combination chemotherapy for cancer have not been successful due to the presence of additional defense mechanisms in the tumor, such as forced DNA repair systems [27].

Mimicry of latent viruses

The mechanisms of viral "mimicry" used by cancer cells are also well known [28,29]. Persistent viruses (herpes, cytomegalovirus, Epstein-Barr virus, papillomaviruses, coronaviruses, HIV, and others) play a leading role in the etiology of many cancers [30–33]. Often, a cancer cell is persistently infected with multiple viruses, and the tumor itself expresses immature Di-particles that lack a

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complete viral genome [34–37]. The mechanisms of viral persistence, exemplified by the Epstein-Barr virus, are well described in the review. Virtually all persistent (latent) viruses have the ability to evade the immune system and shield infected cells from immunity [38–40].

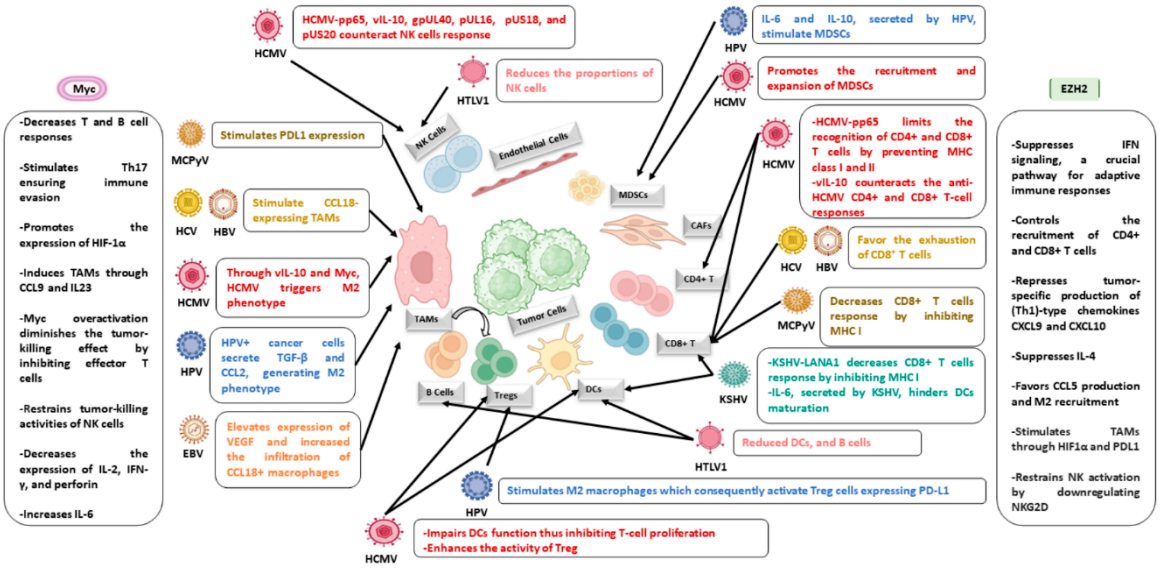

Figure 3. Viral suppression of anticancer immunity (by [41]).

What if such a latently viral-infected cell is a cancer cell? For example, during the latent phase of herpesvirus infection caused by herpes virus types 1 and 2 and herpes zoster, special immunosuppressive T-killer cells specific to a particular virus appear in the body [42]. These cells not only fail to eliminate infected cells but, conversely, protect them from immune-mediated clearance. On the one hand, it is clear that if these viruses persist in nerve cells, the autoimmune process can lead to encephalitis, neuralgia, and other pathologies of the central nervous system (which often occur with these viral infections). However, in most cases, such proviral NK cells promote survival and prevent rejection of infected neurons. One of the best-known types of such pathology is multiple sclerosis, in which the formation of proviral NK cells is prevented by their association with certain human MHC molecules. At the same time, the immune system continues to eliminate all latently infected cells (as demonstrated for Epstein-Barr virus) without restriction, including neurons [43,44]. Now let's move on to cancer cells that are latently infected with viruses. In addition to proviral NK cells, which are typically virus-specific, M2 tumor-associated macrophages are abundant in tumors and protect them from immune attack [45,46]. In fact, two of the most active cell types in the immune system are already switching sides: NK cells and M2 macrophages. Given that CD4 lymphocytes are targets of infection by both HIV and endogenous retroviruses, the lymphokine coordination system via CD4 is deteriorating [47]. In the body of a cancer patient, at least three groups of cells, if not all, are not functioning normally, even if they are not directly protecting the cancerous tumors.

Targeted therapy involves low-molecular-weight drugs or monoclonal antibodies that block specific cancer proteins and mechanisms. Recent studies have shown that, despite high efficacy at the start of therapy, targeted treatment loses effectiveness over time, as does conventional polychemotherapy, due to factors such as tumor heterogeneity and immune responses [48]. In addition, attempts to stimulate the immune system by suppressing immune checkpoints have also failed to completely eliminate cancer cells from the body, although they have been shown to significantly inhibit the growth and metastasis of immune-contrasting tumor types [49].

Key mechanisms of persistent viruses for cancer tumors to evade immune control

Long-term survival of the virus in the host organism requires suppression of the immune response. In the development of virus-associated cancers, the same "proviral" mechanisms become

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tools for tumor defense. To activate T-killers (CD8+), a tumor cell must express fragments of its proteins on the surface in conjunction with MHC-I (HLA-I) molecules [50]. Viruses block this "display window" in several ways: The E5 protein of the human papillomavirus (HPV) retains MHC-I molecules in the Golgi apparatus, preventing them from reaching the membrane [51,52]. Similarly, the LMP2A protein of the Epstein-Barr virus suppresses the synthesis of heavy MHC chains [53,54]. Viral oncoproteins can initiate the degradation of TAP1/2 transporter proteins, which deliver antigens to the endoplasmic reticulum [55]. As a result, the tumor becomes "empty" for T cells. Virally induced tumors are often characterized by the overexpression of molecules that suppress lymphocyte activity. PD-1/PD-L1: E6 and E7 oncoproteins (HPV) activate the PI3K/Akt and STAT3 pathways, which directly increase the density of PD-L1 receptors on the cancer cell membrane [56]. Upon contact with a T cell, this ligand causes the T cell to become anergic (i.e., "fall asleep"). Persistent viral antigenic stimulation leads to the accumulation of T lymphocytes with an exhausted phenotype [57]. Such cells express a whole set of inhibitory receptors (LAG-3, TIM-3, TIGIT) and lose their ability to lyse cells [58,59]. Viruses alter the very biochemistry and genetic accessibility of the cell's defense systems. The hepatitis B virus (HBx protein) stimulates methyltransferase enzymes, which "lock" the promoters of interferon and MHC-I genes [60,61]. This prevents cells from responding to cytokines, even when they are present. The HPV E7 protein activates the IDO1 (indoleamine 2,3-dioxygenase) pathway [62]. This leads to tryptophan degradation in the microenvironment and the accumulation of kynurenine. T cells are extremely sensitive to tryptophan deficiency: under such conditions, they stop dividing and may undergo apoptosis. Viruses create a suppressive "cocoon" of regulatory cells around the tumor. EBV encodes the BCRF1 protein, which is nearly identical to human IL-10 [63,64]. This "viral IL-10" suppresses the activity of dendritic cells and macrophages, preventing the immune response from being triggered. Hepatitis C and B viruses promote the recruitment of Tregs (regulatory T cells) and MDSCs (myeloid suppressor cells) to the liver [65,66]. These cells actively secrete TGF-β, which blocks the activity of natural killer (NK) cells and T lymphocytes.

Table. Some mechanisms by which viruses and cancer cells evade immune control

Mechanism	**Viral agent**	**Cell's effect**
Inhibition of cGAS-STING	HPV, EBV	Absence of interferon production upon detection of viral DNA.
Enhancement of FoxP3+ cells	HTLV-1, EBV	Creation of an immune tolerance zone around tumor nodes.
NF-κB modulation	LMP1 (EBV), Tax (HTLV-1)	Switching macrophages to the pro-tumor M2 type.

The evasion of viral tumors from the immune system is not a passive process, but rather an active reprogramming of the immune landscape by viral oncoproteins. Understanding these mechanisms now allows us to develop combination therapies that combine checkpoint inhibitors with epigenetic and classic antiviral drugs [67–70].

3. Alternative ways to combat resistant tumors

One of the most promising areas in the fight against cancer, especially highly metastatic and resistant forms, is immunotherapy. Dr. Rosenberg's initial experiments with adoptive immunotherapy for cancer yielded remarkable results in metastatic melanoma [71]. The use of

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adoptive immunotherapy led to long-term remissions in patients and, in some cases, even complete recovery [72]. Unfortunately, not all cancerous tumors responded to adoptive immunotherapy. But for the first time, cases of complete tumor regression were recorded using the adoptive cancer immunotherapy method [73,74]. The essence of adoptive cancer immunotherapy is that blood was taken from a specific patient, the lymphocyte fraction was isolated, and the cells were stimulated with interleukin-2. The activated lymphocytes were then expanded and reinjected into the same patient. Activated lymphocytes, particularly NK cells, successfully identified and eliminated the cancer [75]. Until recently, it was not clear why the treatment was only effective in a small number of patients, even those with the same histological type and stage of cancer [76,77]. Only in recent years has the study of tissue rejection mechanisms for successful transplantation revealed that certain immune cells "protect" tumors and metastases from rejection and attack [78,79]. The mechanism of macrophage bipolarity has been particularly well studied. The M1 subtype of macrophages, or pro-inflammatory subtype, is aimed at destroying infections and cancer cells and expresses a set of pro-inflammatory cytokines, while the M2 subtype of macrophages, or anti-inflammatory subtype (pro-tumor), inhibits all anti-infective and anti-cancer immune responses against the tumor [80]. Efforts to develop drugs that convert macrophages from the M2 to the M1 phenotype are ongoing [81,82]. The microecology of tumors contains a substantial number of M2 macrophages, which far exceed the pro-inflammatory M1 phenotype by hundreds of times [83,84]. This explains the limited effectiveness of adoptive cancer immunotherapy across many tumor types and patient populations. Researchers have proposed two main ways to combat tumor immunological tolerance through the M2/M1 mechanism. The first approach is aimed at the specific destruction of M2 cancer macrophages (lytic pathway) [85]. The second approach is designed to directly stimulate the transformation of M2 macrophages into M1 macrophages within the tumor (the transforming pathway) [86]. In both cases, the initial experiments were promising, yielding effective selective inhibitors of M2 macrophages and activators of the M2-to-M1 phenotype transformation. None of the proposed drugs have yet reached phase 2 clinical trials. However, focusing solely on macrophages is a one-sided solution, as the role of viruses in masking the cancer cells they infect has not been taken into account, nor have other pro-tumor cells of the immune system (pro-tumor NK and T-killers, infected with endogenous CD4 retroviruses, and other factors) were not taken into account.

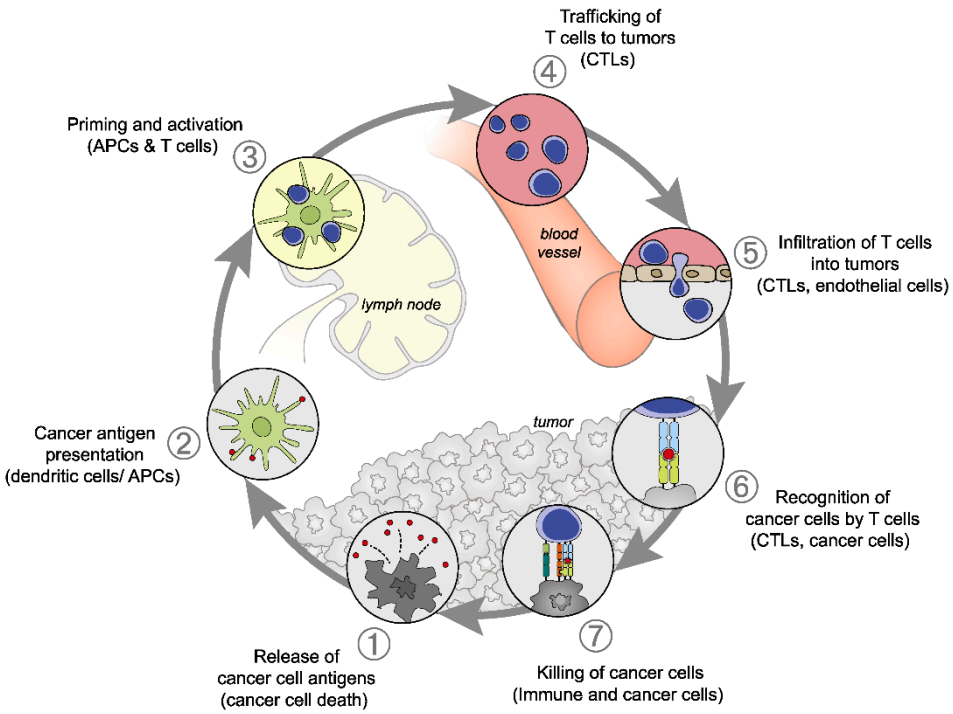

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Figure 4. Cancer-immunity cycle: (1) Release of cancer antigens from tumor cells; (2) Presentation of cancer antigens on the major histocompatibility complex class (MHC) by antigen-presenting cells; (3) recognition of cancer antigens on the MHC by the T cell receptor, resulting in T cell activation; (4) Trafficking of activated T cells; (5) Infiltration into the tumor; (6) Recognition of cancer antigens on the MHC within the tumor; (7) Attack on tumor cells, resulting in tumor cell injury/death. This figure was adopted from Chen DS et al.[87].

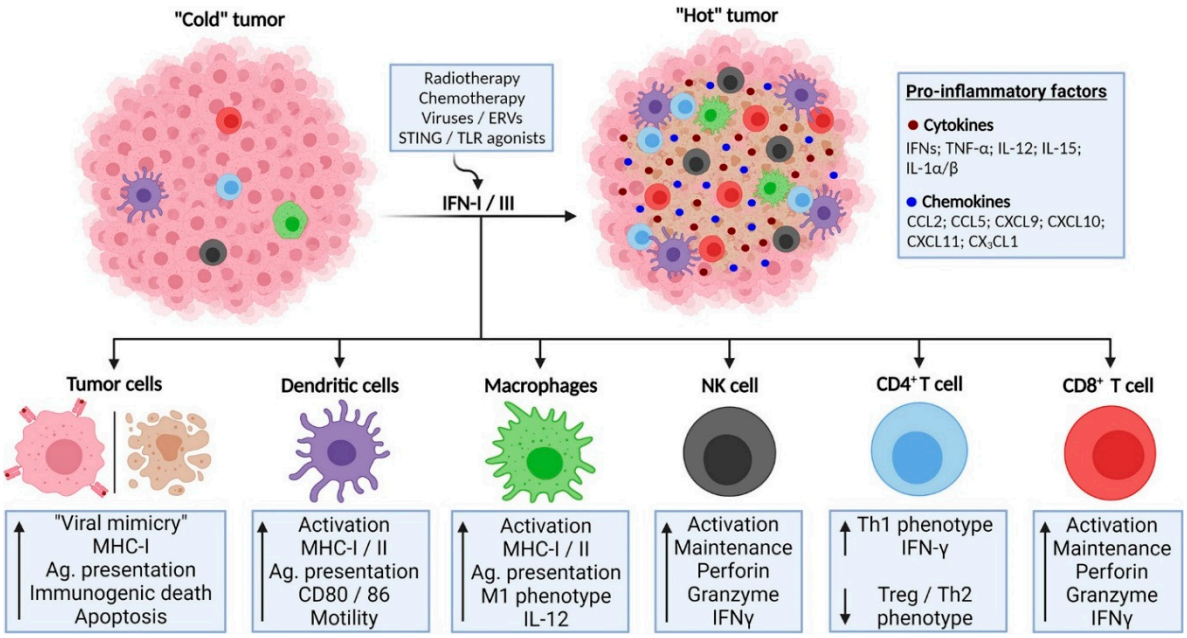

Figure 5. Activation of IFN-I/III responses in TME lead to enhanced anti-tumor response and tumor control. Poorly immunogenic ("cold") tumors might be converted to highly infiltrated tumors ("hot") through the activation of IFN-I/III responses. This might be accomplished through several strategies, such as genotoxic therapies and triggering of innate immunity receptors involved in antiviral responses. IFN-I/III mediates this phenomenon by its actions on tumor cells, inducing immunogenic cell death and enhanced antigen presentation as well as by its effects in activating anti-tumor immune cell populations, such as dendritic cells, T lymphocytes, and natural killer (NK) cells (cited by [88]).

Ratio of clone cell numbers

The main problem with all types of immunotherapy remains the imbalance between the number of cancer cells and immune cells. Cancer cells are significantly more numerous (hundreds of times more) and multiply much faster in stages 3-4 of the disease. Accordingly, even if the immune system begins to recognize the cancerous tumor during immunotherapy, it will not be able to destroy it completely [89,90]. For the immune response to be effective, it is first necessary to halt tumor growth without damaging immune cells. Classic chemotherapy acts equally on both cancer cells and immune system cells, slowing tumor growth and cell division [91].

Thus, you have come up with a description of the "ideal" anti-cancer drug, which would take into account all the characteristics of the tumor, all clones - generations of tumors, the microenvironment of tumors, the characteristics of the patient's body, the stage and histology of the tumor, and the properties of tumor immunity. On the one hand, personalized therapy is one way to solve the problem of cancer treatment, but on the other hand, the above-mentioned problems are not solved by prescribing a personalized drug; the risk of the toxic effects of chemotherapy on the whole body can be reduced by selecting a personalized, effective drug (at the beginning of treatment).

The ideal cancer treatment plan

Based on the above, the ideal anti-cancer therapy regimen would combine methods to inhibit tumor growth, immunotherapies, and specific antiviral drugs to restore immune function. The combination of existing classical methods of chemotherapy and immunotherapy has not yet yielded

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the expected results due to the contradictions outlined above: the simultaneous effect of chemotherapy on cancer and immunity, the adaptation of cancer cells to chemotherapy through universal mechanisms (induction of P-glycoprotein expression and phosphorylation of the DNA repair apparatus), single mutations in immune checkpoint genes and target drug genes, and the persistence of latent viruses in both tumor cells and immune system cells.

The ideal anti-cancer chemotherapy drug

What could be the properties of such a chemotherapeutic drug? First, to prevent the tumor from adapting to it, its effect on DNA must be neutralized. Currently, most anticancer drugs are either DNA mononucleoside antimetabolites [92] or bis(beta-chloroethyl)amine derivatives that cause DNA strands to cross-link [93–95]. A living organism—a cancer cell—easily overcomes this effect by activating the DNA repair system [96]. Most of these drugs are also low-molecular-weight compounds that are easily "ejected" from the cell by activated glycoprotein-P [97]. Thus, the drug must inhibit cancer cell division without fundamentally affecting the cell nucleus and DNA, and be larger than, for example, cisplatin or fluorouracil, getting stuck in the glycoprotein-P channel. There is another system in the cytoplasm that fundamentally lacks a repair system: ribonucleic acids. RNA primarily facilitates protein synthesis: active genes are transcribed into messenger RNA, which is transported to the cytoplasm and translated on ribosomes. Transport RNAs carry individual amino acids to the polyribosome, where protein is synthesized, and ribosomal RNA is the "factory" for protein assembly. There are also many regulatory small RNA fragments in the cytoplasm called microRNAs [98]. All of this RNA machinery has no repair systems. If it is simultaneously used as a target for a new anticancer drug and then blocked, the cell cannot escape by mutation or repair [99]. A mutation with a change in one RNA will not help, since the targets of the drug are all the RNAs of the cancer cell. There is simply no repair system for RNA per se. The target should not be a single point, not a single specific RNA (as with targeted drugs), but all RNA molecules—transport, matrix, ribosomal, and regulatory.

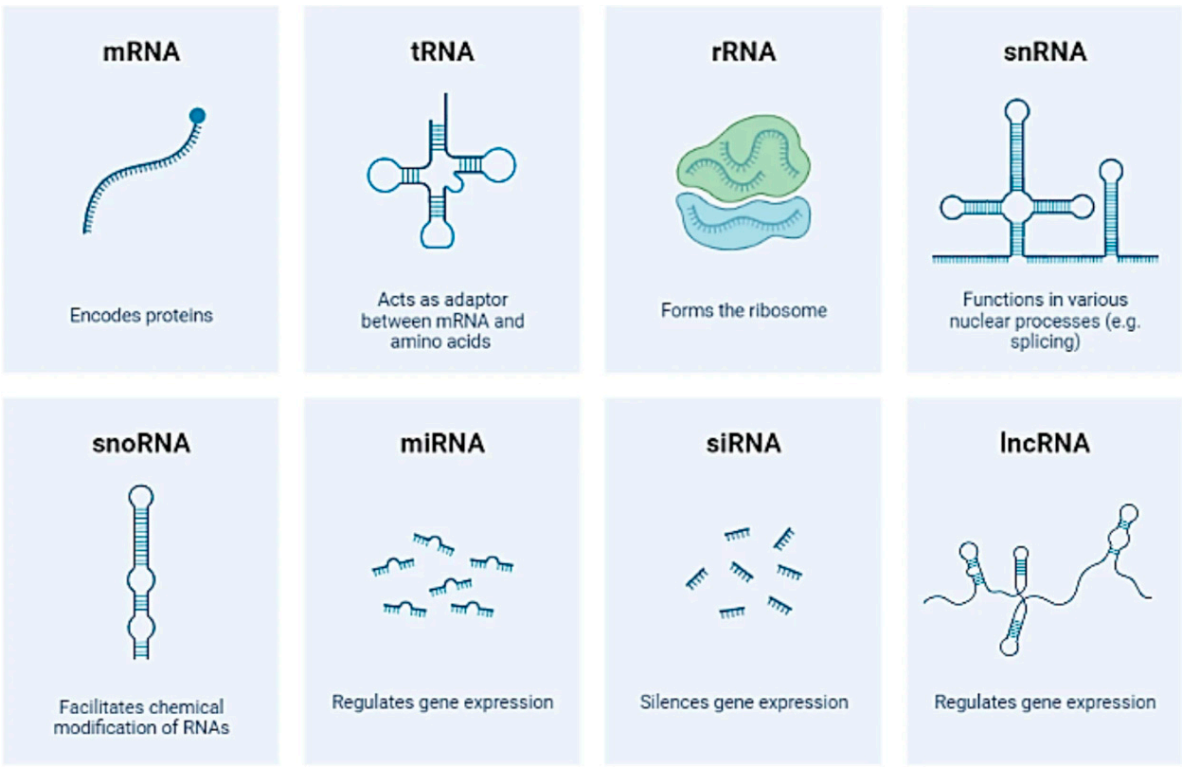

Figure 6. Diversity of RNA Types and Their Functionalities in a Cell. This comprehensive diagram illustrates the various types of RNAs produced within a cell, showcasing their distinct functionalities and roles. It highlights messenger RNA (mRNA) as the template for protein synthesis, transfer RNA (tRNA) responsible for delivering amino acids to the ribosome during translation, ribosomal RNA (rRNA) as a structural component of

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ribosomes, small nuclear RNA (snRNA) involved in RNA splicing, small nucleolar RNA (snoRNA) participating in ribosomal RNA modification, microRNA (miRNA) regulating gene expression, long non-coding RNA (lncRNA) contributing to diverse cellular processes, small interfering RNA (siRNA) engaging in RNA interference, and other RNA species with specialized functions, providing a comprehensive overview of the functional diversity of cellular RNA molecules [100].

However, in this case, there is a problem with the lack of selectivity of such a drug specifically for cancer cells [101,102]. Will this drug inhibit protein synthesis in healthy, non-tumor tissues? Accordingly, it is necessary to select a property of cancer cells that distinguishes them from healthy cells. One such property of cancer is its rapid growth. To ensure this, cancer cells need a huge amount of "building material," namely RNA and DNA nucleosides [103,104]. However, there are clearly insufficient mononucleosides in the blood and intercellular matrix to support cancer cell division, and more than 90% of cancerous tumors have activated a mechanism of increased micropinocytosis [105,106]. They capture not only mononucleosides and mononucleotides by active transport, but also oligonucleotides and sometimes polynucleotides as "food" through activated macropinocytosis. This property captures suspensions of micro- and nanoparticles and biopolymers. This property has long been exploited by the pharmaceutical industry to enhance the selectivity of anticancer drugs, increase their accumulation in cancer, and reduce their systemic toxicity [107]. Drugs are administered orally or into the membranes of vesicles, liposomes, PEG-modified liposomes, polymeric nanoparticles, and other nanosuspensions, which are easily captured by cancer cells and are practically not captured by normal healthy cells (except for macrophages). Doxorubicin in liposomes (e.g., Lipodox) and cisplatin (Lipoplatin) in liposomes are quite successful in treating early-stage cancer and allow patients with non-metastatic cancers to be cured, while significantly reducing their toxicity to healthy tissues [108]. However, these drugs still primarily affect DNA and a single target (doxorubicin). This is why the effects of these drugs are readily overcome by cancer cells through point mutations, increased expression, amplification of the glycoprotein P gene, and activation of genome repair systems.

The MoLRx binary system and Lipo-Liasten

We approached the problem from the perspective of G. Altshuller's Theory of Inventive Problem Solving [109,110]. It was necessary to resolve several contradictions: chemotherapy should target cancer cells without affecting normal tissues, and it should suppress M2 macrophages, pro-tumor NK cells, and T suppressors. When combined with immunotherapy, it should not interfere with it. Suppressing and not suppressing macrophages is the main contradiction. An additional contradiction is to suppress the proliferation of dividing cells and prevent resting cells from dividing, thereby reducing the extent of cancer metastasis. To do this, we proposed dividing the therapy into two time intervals. The binary nature of the scheme includes the first stage—suppressing the growth of cancer cells with a multi-target system that blocks the functions of the entire RNA pool of the cell and suppresses the functions of M2 macrophages—and the second stage—stimulating the transformation of macrophages with the M2 phenotype into macrophages with the M1 phenotype. An additional component of the system may include one or more antiviral drugs, including those that inhibit herpesvirus replication and those that inhibit retroviral reverse transcriptase. The disadvantage of reverse transcriptase inhibitors and other drugs for the treatment of AIDS is their very slow action—sometimes it takes years to restore normal CD4 function. This approach is not applicable to patients with cancer. The remaining targets are M2 macrophages, pro-tumor NK cells, and T suppressors.

MoLRx

Although the mechanism of selective action on cancer cells is more or less understood in principle—selective accumulation through macropinocytosis—the use of all RNA in the cell as targets is a rather complex task. To obtain a drug that blocks all RNA in a cancer cell, a similar but antisense RNA is needed. In addition, it must be resistant to the action of cancer cell ribonucleases. Furthermore, for such a multi-target effect, the entire RNA pool of a eukaryotic cell will be needed for conversion to antisense. We have developed a technology for converting DNA and RNA into their

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antisense counterparts while maintaining high hybridization selectivity for the original molecules. To this end, we proposed modifying the structure of the finished RNA molecule (or DNA) by acylation and/or alkylation of exocyclic and some endocyclic amino groups in the nucleotide structure that are available for modification [111–113].

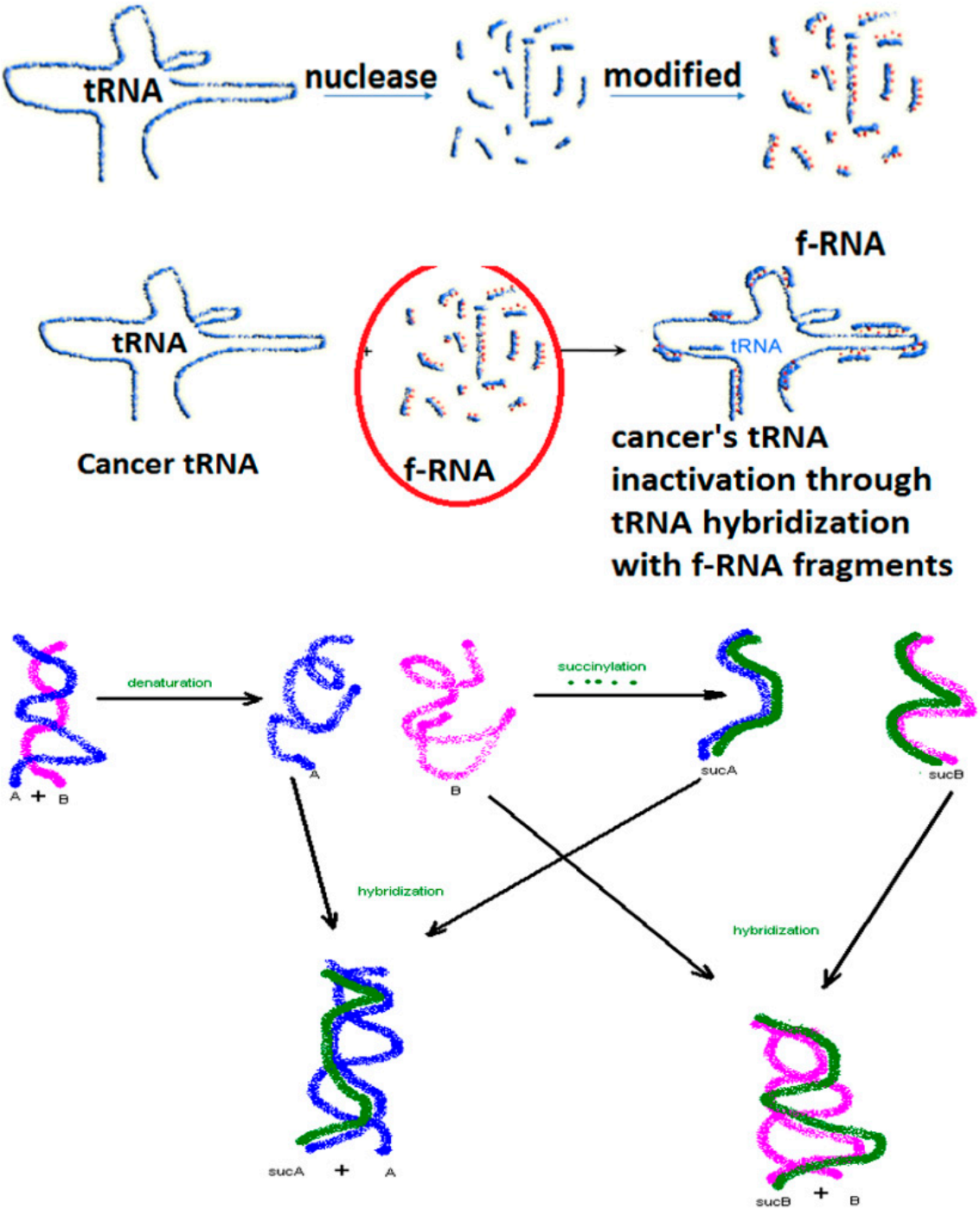

Figure 7. Synthesis and mechanism of action of the MoLRx.

As a result of this modification, the nucleotide sequence in RNA or oligo-RNA remains the same as in the target itself, but the principle of bond formation changes to hydrogen-ionic (the initial bond between RNA/DNA chains is exclusively hydrogen-based), and the charges change to opposite ones. At the same time, helicases and nucleases are unable to unwind the double helix with atypical bonds after hybridization of the initial RNA with antisense oligomeric fragments. Where can we get the entire pool of eukaryotic RNA? We proposed using the entire pool of yeast RNA for this purpose.

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Moreover, the technology for obtaining the acidic form of RNA from yeast is well-studied and is available on Sigma-Aldrich websites [114,115]. We first fragmented yeast RNA into oligomeric fragments with ribonuclease, then modified their structure by double acylation/alkylation to replace the charge with the opposite one. Due to the oligomeric structure of its components, this modified mixture is also captured by the tumor via macropinocytosis. In addition, this antisense-oligo-RNA mixture is captured by macrophages through the same macropinocytosis. Macrophages do not die in the process; rather, their activity decreases, which is particularly important for inactivating the function of M2-phenotype cancer macrophages. Because of their relatively large size, when this mixture of antisense oligo-RNA enters the body, it is captured by cells that exhibit increased macropinocytosis, particularly cancer cells. Healthy cells lack this property (they capture only mononucleotides). Because such antisense oligonucleotides can find and hybridize to their target, they bind to and inhibit the entire pool of cellular RNA, thereby stopping protein synthesis. The drug's effect is reflected in the complete cessation of tumor growth and metastasis, returning them to the levels observed at the beginning of treatment. Sometimes the immune system begins to destroy cancer cells on its own, and the tumor and metastases decrease, although the drug is intended only to inhibit protein synthesis and, accordingly, cell division. We did not plan to create a drug that would cause the death of cancer cells. This is because in stage 3-4 cancer, any massive death of cancer tumor cells and metastases will cause the well-known tumor lysis syndrome [116]. This is a well-known phenomenon where a patient is given a new effective drug, the tumor is rapidly destroyed, and the patient dies of acute renal failure because the products of tumor decay mainly "kill" the kidneys through lactic acid overload.

Lipo-Liasten

Accordingly, it is necessary to first halt tumor growth without causing massive cell death and, in the second stage, stimulate the immune system to lyse the tumor via apoptosis and ferroptosis, thereby excluding rapid necrosis. To this end, we proposed to "remove" the protection of the tumor from pro-tumor M2-phenotype macrophages, T-suppressors, and NK cells. The latter two cell groups are closely related to the M1 macrophage signaling system. If M2 phenotype macrophages are transformed into M1 phenotypes without killing them, NK cells will also acquire anti-cancer phenotypes, and T-suppressors will switch to another target and leave the tumor. To convert M2 macrophages into M1 macrophages, we use the same macrophage phagocytosis protocol; as a stimulant, we use the pentamuramyl peptide [117–119].

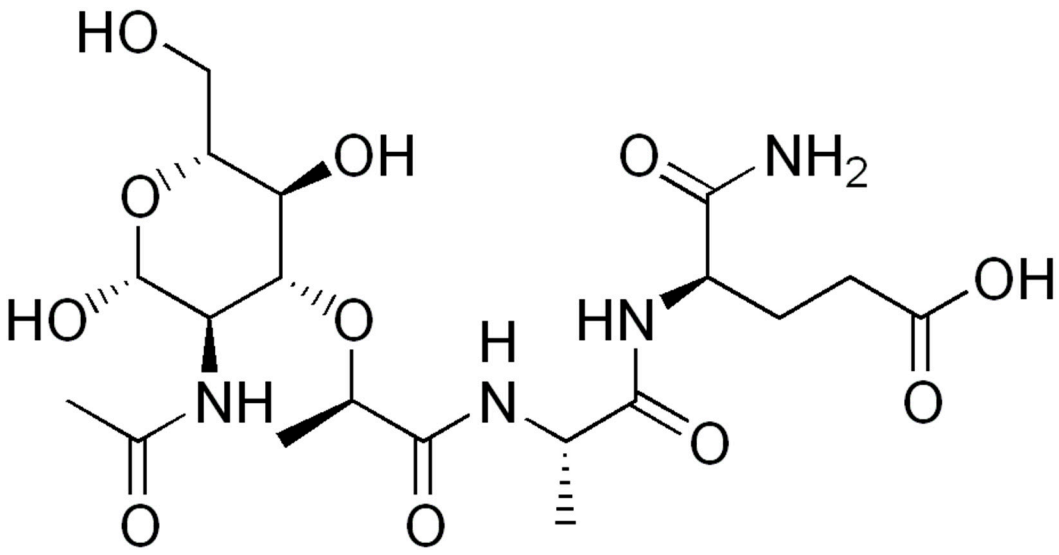

Figure 8. Main structure of the muramylpeptide.

We dynamize the latter by alkylation/acylation/phosphorylation of the structure, forming thousands of epitopes on the same pentamuranyl peptide core [120,121]. The stimulating capacity of

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such a product is 1,000 times that of pure muramilpeptid (liasten) and allows its reduction in the final product by 100-fold without reducing its activity. The introduction of acyl-lipidistan into liposomes reduces the risk of autoimmune pathologies and ensures selective accumulation in macrophages. Under its influence, M1 macrophages become more active and mobile, and M2 macrophages are transformed into M1 macrophages. Thus, if the immune system is continuously stimulated with Lipoliasten, in the context of a cessation of tumor growth, with the parallel use of MoLRx, the immune system can completely lyse the tumor and detect all metastases.

Immune deficiencies in cancer patients

The problem of latent viruses persisting in immune system cells and cancer cells remains unresolved. It is well established that viruses play a significant role in the etiology of cancer, both as oncogenic agents that cause malignancy and as latent agents that trigger and facilitate cancer evading immune control.

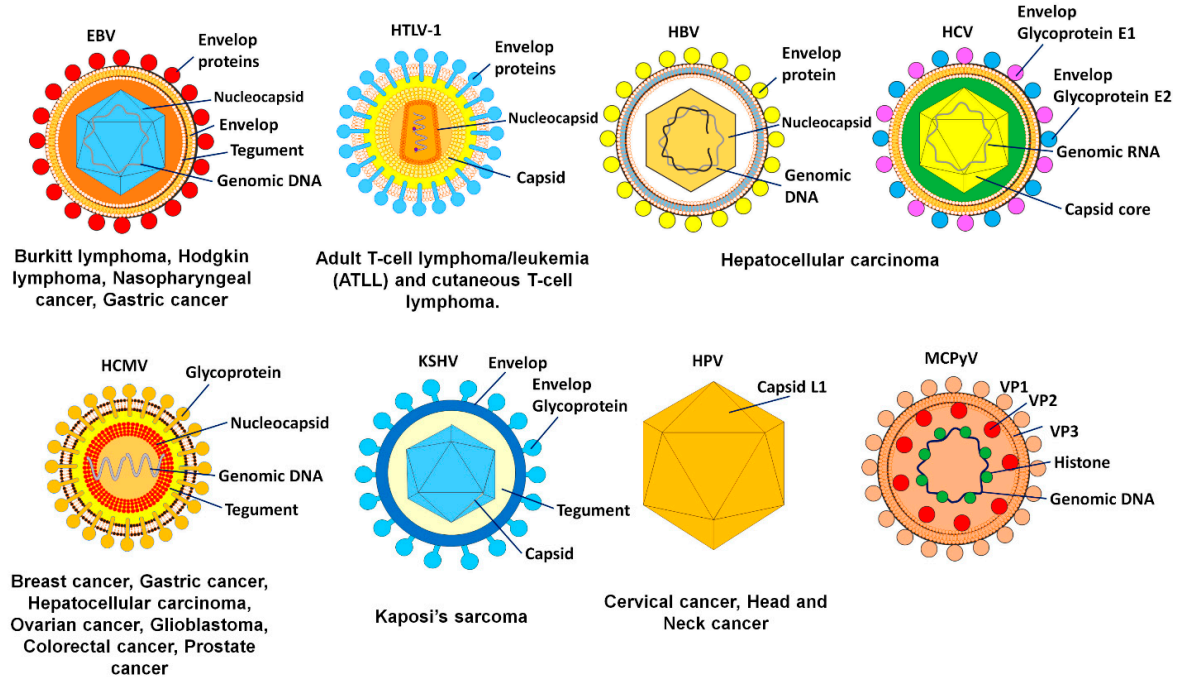

Figure 9. The oncogenic viruses with their target tissues and consequent malignancies [122].

No antiviral drugs are effective against latent viral forms (viral depots) [123]. Drugs for treating HIV are only effective during the active replication phase of the virus, and they act very slowly. Within 1-2 years, in 90% of cases, HIV/AIDS patients are unable to fully restore the level of CD4 helper lymphocytes, which are the target for the replication of this virus [124]. Cytomegalovirus and Epstein-Barr virus are lymphotropic viruses. B-lymphocytes and plasma cells are particularly sensitive to EBV. When immune cells are infected with such viruses, the cells themselves acquire "protection" and do not die; they are not affected by interferon and other normal immune components [125,126].

Although the binary scheme overcomes most unresolved problems—tumor adaptation to chemotherapy, multitargeting, and activation of the immune system against tumors—the task of combating latent, persistent viral infections that block the immune response to cancerous tumors remains unresolved. Ways to address the human immunodeficiency virus are well described in the review. So far, none of the approaches to combating latent viruses has been implemented and widely applied, but research continues.

Summary

Current cancer therapies, including targeted drugs and immune checkpoint inhibitors, often fail due to rapid tumor adaptation, P-glycoprotein-mediated drug efflux, and the lack of effective targets

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in dormant metastatic clones. Furthermore, latent viral infections and pro-tumor M2-phenotype macrophages create an immunosuppressive "cocoon" that shields tumors from the immune system.

This study introduces a novel binary therapeutic system designed to overcome these challenges. The first component, MoLRx, uses a technology that converts the entire yeast RNA pool into antisense oligo-RNA via acylation and alkylation of nucleotide bases. These structures selectively accumulate in cancer cells via overactivated macropinocytosis and hybridize with the cell's entire RNA pool (mRNA, tRNA, rRNA, and regulatory RNA) using stable hydrogen-ionic bonds. Because RNA lacks a dedicated repair system, this multi-target approach effectively halts protein synthesis and tumor growth without inducing the rapid necrosis associated with tumor lysis syndrome.

The second component, Lipo-Liasten, addresses immune evasion by transforming tumor-associated M2 macrophages into the pro-inflammatory M1 phenotype. This is achieved using a modified pentamuramyl peptide encapsulated in liposomes, which reactivates anti-cancer NK cells and eliminates the protective effect of T-suppressors. By combining growth inhibition with immune reactivation, this binary system offers a comprehensive strategy for treating resistant and metastatic cancers while circumventing traditional mechanisms of resistance.

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