UNIVERSIDADE DA CORUÑA

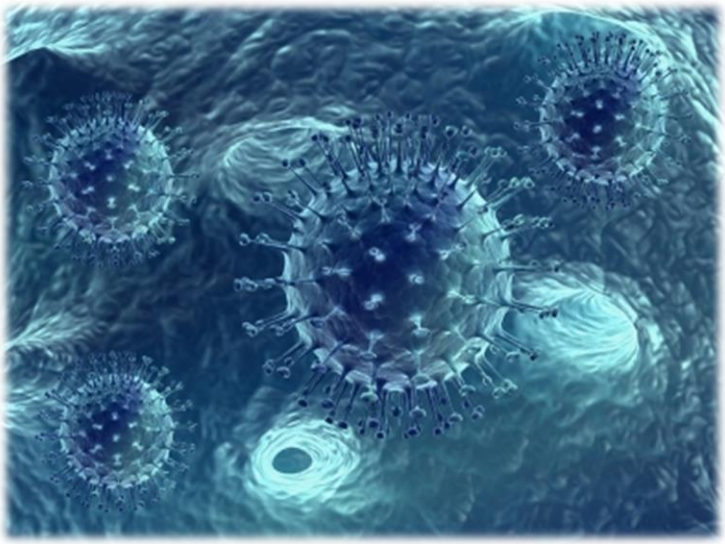
Grao en Bioloxía

MEMORIA DO TRABALLO DE FIN DE GRAO

Revisión bibliográfica: Virus e cancro

Revisión bibliográfica: Virus y cáncer

Literature review: Virus and cancer



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CONTENTS

ABSTRACT

Cancer is one of the main causes of global mortality, and even though it is considered to be a non-communicable disease, several infectious agents have been found to contribute to oncogenesis through both indirect and direct mechanisms. Viruses stand out among all the different oncogenic microorganisms, as they are estimated to participate in 20% of all human cancers. However, some viruses, the so-called oncolytic viruses (OVs), can be used as specific therapeutic agents in cancer treatment. OVs are the basis of viral oncotherapy, and are responsible for specifically targeting and killing cancer cells selectively, leaving the surrounding non-malignant cells unharmed.

KEYWORDS

Cancer, oncogenic viruses, oncolytic viruses (OVs), cancer treatment, viral oncotherapy.

RESUMEN

El cáncer es una de las principales causas de mortalidad global, y aunque se considera una enfermedad no transmisible, se han detectado numerosos agentes infecciosos que contribuyen a la oncogénesis por medio de mecanismos directos e indirectos. Los virus destacan entre todos los diferentes microorganismos oncogénicos, ya que se estima que participan en el 20% de la totalidad de los cánceres humanos. Sin embargo, algunos virus, los denominados virus oncolíticos (VOs), pueden ser utilizados como agentes terapéuticos específicos en el tratamiento del cáncer. Los virus oncolíticos son la base de la oncoterapia viral, y su principal función es detectar específicamente y matar selectivamente las células cancerosas sin perjudicar las células no malignas circundantes.

PALABRAS CLAVE

Cáncer, virus oncogénicos, virus oncolíticos (VOs), tratamiento del cáncer, oncoterapia viral.

RESUMO

O cancro é unha das principais causas de mortaldade global, e aínda que é considerado unha enfermidade non transmisible, verificouse que varios axentes infecciosos parecen contribuír no proceso de oncoxénese por medio de mecanismos directos e indirectos. Os virus destacan entre todos os diferentes microorganismos oncoxénicos, xa que se estima que participan no 20% da totalidade dos cancros humanos. Sen embargo, algúns virus, os denominados virus oncolíticos (VOs), poden ser utilizados como axentes terapéuticos específicos no tratamento do cancro. Os virus oncolíticos son a base da oncoterapia viral, e a súa principal función é detectar especificamente e matar selectivamente as células cancerosas sen prexudicar as células non malignas veciñas.

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Cancro, virus oncoxénicos, virus oncolíticos (VOs), tratamento do cancro, oncoterapia viral.

1. INTRODUCTION

Cancer is one of the major diseases affecting a large proportion of the world's current population. Despite the significant advances in cancer therapies over the past few decades the high mortality rate of cancer persists, causing about one in every seven deaths worldwide [1]. Cancer arises from uncontrolled cell division with potential metastasis into the healthy neighbouring tissues. This disease can be triggered by internal factors (such as immunity, severe hormonal changes and inherited genetic disorders), external factors (such as poor diet and unhealthy lifestyles or habits) and environmental factors (like exposure to chemicals, radiation, pollution, and infectious organisms) [1] and in some cases it is diagnosed after years of exposure to these factors.

Although it is considered to be a non-communicable disease, several infectious agents have been found to contribute to oncogenesis through both indirect and direct mechanisms. There is a large number of oncogenic microorganisms, but viruses stand out among them all. Even though the great majority of animal viruses are not oncogenic, there is evidence that a large number of viruses participate in 20% of human cancers. Some viruses have been labelled as carcinogens by the International Agency for Research on Cancer (IARC): hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomavirus (HPV) and Epstein-Barr virus (EBV) [2].

Today, there are different cancer treatments available, being chemotherapy and radiotherapy the two most representative. However, these therapies do not always block excessive cell proliferation and metastasis, and they can harm healthy cells and favour the evolution of malignant cells with higher drug resistance [3]. Targeted cancer therapies are a more effective approach, since they target tumour cells without affecting the normal cells. Some viruses, known as oncolytic viruses (OV), can be used as specific therapeutic agents in cancer treatment. With advanced biotechnological and molecular methods it is possible to molecular engineer these viruses as targeting elements with higher selectivity. Oncolytic viruses are the basis of viral oncotherapy, a new cancer treatment that uses tumour-selective OVs that target and kill cancer cells selectively, leaving the surrounding non-malignant cells unharmed and effectively delivering the cancer treatment. Nowadays it is known that it is possible to combine traditional cancer treatments with viral oncotherapy, consequently obtaining better results [3].

2. CURRENT PERSPECTIVE

Cancer is a growing problem in today's society. The chances of developing this disease are increasing, and the mortality rate of cancer persists despite the great improvements in therapies over the past few decades. Even though it has been estimated that most cancer cases in developed nations are due to unhealthy behaviours, there is still a high percentage (16.1%) of cancers directly caused by

infections; the vast majority of which (80%) appeared in less developed countries [2].

The growing likelihood of developing cancer makes it necessary to improve the different therapies applied in cancer treatment. Viral oncotherapy seems to be a suitable approach to this problem, as viruses have proven to be effective vaccination vectors and are now developed as antitumor agents with the capability of activating lytic activity and antitumor immune responses [3].

This bibliographic compilation, therefore, intends to emphasize the importance of viruses as infective agents capable of producing cancer, especially in the case of less developed countries. Another objective of this work is to show the growing importance of viral vectors as effective therapeutic agents for cancer treatment.

3. ONCOGENIC VIRUSES

A lot of viruses have oncogenic potential in animals. However, the relationship between these infective agents and the development of tumours in humans has only been demonstrated in some cases. The ways through which viruses can contribute to carcinogenesis are very different, but they can all be grouped in two types of mechanisms, direct and indirect; however, sometimes it is very difficult to precisely define if the development of the tumour is due to a direct or an indirect mechanism [4].

Human papillomavirus (HPV), Epstein-Barr virus (EBV) and hepatitis B virus (HBV) are just a few examples of those viruses that can directly induce carcinogenesis. Tumours are caused by the expression of specific onco-proteins that play a role in cell transformation: inhibiting apoptosis, enhancing cell immortalization and disrupting cell-cycle check-points. In addition, oncogenesis can be indirectly associated with a virus-induced chronic inflammation, as in the case of hepatitis C virus (HCV); in this case, inflammatory mediators and free oxygen radicals are released, which promote tumour vascularization and survival while having direct mutagenic effects [2].

When analysed globally, it is clear that there is an uneven worldwide distribution of the cases of cancer caused by microorganisms. About 16.1% of all cancer cases are caused by infections, 80% of which appeared in less developed nations [2]. Among them, HBV, HCV and HPV cause 95% of infection-associated cancer cases. The mechanisms through which some of these viruses induce the formation of tumours in humans will be discussed below.

3.1. Epstein-Barr Virus (EBV)

EBV is a member of the herpesvirus family that was the first human virus to be directly associated with tumour formation. Its envelope contains a DNA core that is surrounded by an icosahedral capsid [5]. Nowadays, it is known that EBV

infects >95% of the world's adult population [2], and after the infection takes place the individual remains a life-long carrier of the virus [5].

This virus is transmitted by salivary contact, and in the host cell EBV can establish two different types of infection: latent and lytic. It has been associated with several types of human cancers, such as nasopharyngeal carcinoma (NPC), Hodgkin's disease, Burkitt's lymphoma, etc. [5].

To be oncogenic EBV must establish latent infection in B-lymphocytes, so that its viral DNA stays within the cell; the viral DNA is maintained in the host either by its integration into the genome of the lymphocyte or as a circular episome, being therefore transmitted to cell progeny when the host cell replicates. The virus must also avoid killing the host cell, prevent it from becoming a target of the immune system and activate those pathways involved in cell growth control [5].

Latent EBV genes induce an activated phenotype in the infected B-cells, which can be turned into cancerous cells when these latent genes acquire oncogenic mutations. In non-immunosuppressed individuals, the response of cytotoxic T-cells against latent viral proteins prevents the expansion of these activated cells [5]. The EBV latent membrane protein 1 (LMP1) is an essential onco-protein that ensures the immortalization of the infected B-cells [6].

The viral lytic cycle plays an important role in carcinogenesis. Activated cells can intermittently enter this phase of the viral cycle in which viral replication takes place, accompanied by the suppression of host protein synthesis. The resultant cell lysis causes the release of the virions, ensuring EBV transmission to the surrounding cells and therefore increasing the number of latency-infected B-cells. Viral persistence and propagation is also promoted by the extensive methylation of both the host and the viral genome that comes with EBV infection [4].

Nowadays it is known that EBV can shape the microenvironment so that it favours cell transformation. Moreover, some of these lytically-infected B-lymphocytes release oncogenic cytokines and growth factors, promoting carcinogenesis, angiogenesis and metastasis [6].

3.2. Human Papillomavirus (HPV)

Infection with Human Papillomavirus (HPV) is very common in worldwide human populations. Although this virus causes several different types of genital cancers, most of them have a low incidence rate [2]. Despite that, invasive cervical carcinoma is still one of the most common cancers in women, and it is caused by the transformation that the cervical epithelium suffers during persistent HPV infections [7].

There are approximately 200 types of this small double-stranded DNA virus, but only some of them are pathogenic and lead to malignant diseases in the epithelial

cells they infect. In particular, HPV types 16 and 18 cause nearly 60-80% of all cervical cancer cases [7].

In the case of cervical cancer, two pre-requisites for its development are the infection and the colonisation of the cervical epithelium. However, it seems that the immune response plays an important role in the development and final outcome of the disease [7]. The important influence of the immune system is clearly confirmed in the case of immunosuppressed individuals, in which the prevalence of HPV infections and their associated diseases are more common [4].

3.3. Viral Hepatitis

Hepatocellular carcinoma (HCC) is the most common form of liver malignancies, and it is considered to be one of the most prevalent cancers among humans. Two of the most important risk factors worldwide for the development of HCC are viral hepatitis and alcohol consumption [8]. The development of this cancer is very common in patients with chronic liver diseases like cirrhosis (Figure 1), which can be caused by HBV and HCV [9]. However, the development of HCC in the absence of cirrhosis confirms that both HBV and HCV may be carcinogenic [10]. This explains why most HCC cases are found in those areas where hepatitis viruses exhibit high endemic levels, as is the case of underdeveloped countries [11].

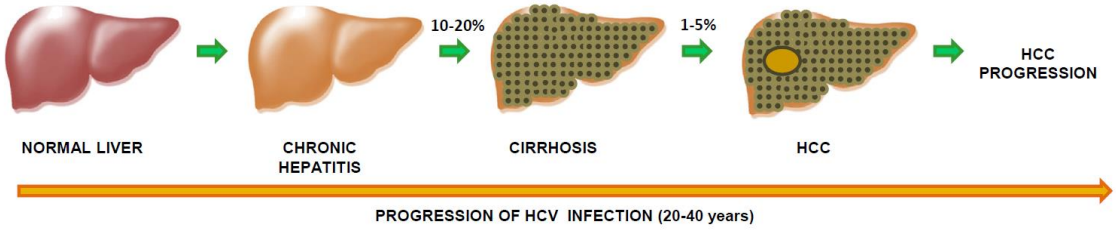

Figure 1: Cirrhosis-mediated carcinogenesis in viral hepatitis 1 [12]

Stages from hepatitis B virus or hepatitis C virus infection to hepatocellular carcinoma. Hepatocarcinogenesis is a multistep process that can last for years. Accumulation of genetic alterations can lead to the malignant transformation of hepatocytes and hepatocellular carcinoma, which is also induced by chronic liver injuries like cirrhosis.

Something that greatly differentiates the two viruses is the impact of cirrhosis over HCC development. Cirrhosis is more strictly associated to HCV-induced HCC, although there have been cases of patients chronically infected by HCV that still developed HCC in the absence of cirrhosis [13].

One common feature of HCC is genomic instability; the accumulation of genetic alterations during hepatocarcinogenesis changes the signal transduction network [14]. Moreover, it is known that the microenvironment originated as a result of chronic inflammation supports tumour initiation, invasion and metastasis [15].

However, although the precise mechanism through which infections caused by hepatitis viruses lead to HCC development is still unknown, it has been reported that overexpression of inflammatory cytokines contributes to tumour development [11].

3.3.1 Hepatitis B Virus (HBV)

Hepatitis B virus (HBV) is a DNA virus that can have eight different genotypes (A to H), each one based on the genomic sequence divergence and all of them with a different geographical distribution. The genotype that has shown the highest risk of HCC is genotype C [8].

Although hepatitis B can be transmitted through contaminated blood transfusions and sexual contact, vertical transmission from mother to foetus continues to be the leading cause of HBV worldwide [8]. Most cases of HBV-related HCC occur in cirrhotic livers, and the risk of tumour development in this conditions are especially important in those regions in which HBV is endemic [10].

HBV can induce hepatocarcinogenesis by both indirect and direct pathways. In the first case, by infecting liver cells HBV incites the accumulation of potential critical mutations in the host genome, resulting in the malignant transformation and clonal expansion of hepatocytes [10].

Likewise, HBV is an oncogenic virus. The integration of its double-stranded DNA at multiple random sites of the host's genome during the first steps of infection can have several mutagenic consequences. These mutations can directly cause HCC in case they provide a selective growth advantage to the infected liver cells. This way the viral DNA ensures its persistence within the host, and the risk of suffering HCC increases along with the levels of HBV DNA in the cell [10].

The most commonly integrated gene is the *HBx* gene, which is intimately related to hepatocarcinogenesis [16].The hepatitis B virus X protein (HBx) is a soluble and multifunctional protein expressed both in the nucleus and the cytoplasm of host cells [16]. It interacts with the different components of the tumour microenvironment, promoting cell proliferation and apoptosis through its influence over cellular signalling pathways [15]. In addition, by binding to wild-type p53 HBx is able to limit its functions and inhibit p53-mediated apoptosis [13].

The *HBx* gene is easily mutated. The most remarkable of its mutations, because of its recurring presence in samples of HCC, is the deletion of the C-terminal tail of the HBx protein. The protein resulting from this mutation retains its functionality and favours malignant transformations [15].

Since the immune system is so tightly associated with tumour formation, cancer cells must have developed different mechanisms to avoid the immune response. HBx contributes to the malignant transformation of hepatocytes by attenuating

the host immune response, upregulating inflammatory cytokines and lengthening HBV infection. All this creates the perfect tumour microenvironment for HCC initiation and metastasis [15].

3.3.2. Hepatitis C Virus (HCV)

Hepatitis C Virus (HCV) is a positive single-stranded RNA virus that shows high genetic variability [8]. In contrast to HBV, the HCV genome cannot be integrated into that of the host cell, as it lacks a reverse-transcriptase enzyme [14].

Once infected with HCV, most patients end up developing Chronic Hepatitis C (CHC). HCC development takes place almost exclusively when the liver is under cirrhotic conditions, and the risk of HCC in chronic patients is higher in those with advanced fibrosis or cirrhosis [9]. Since HCV is a completely cytoplasmic-replicating virus that does not integrate its genome into that of the host, HCC is mainly induced through indirect pathways via chronic inflammation and hepatocellular injury. This is why the presence of cirrhosis is almost mandatory for HCV-induced HCC [14]. However, various HCV proteins have been shown to have oncogenic properties that allow HCV to directly induce HCC by altering several host regulatory pathways (Figure 2) [12].

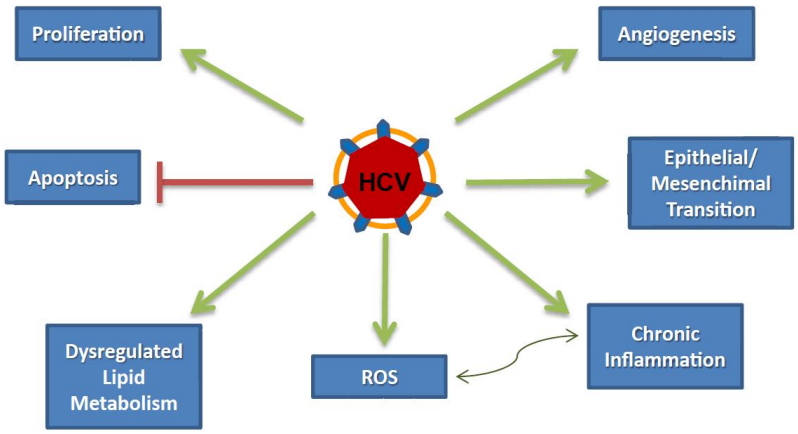

Figure 2: HCV-related mechanisms of carcinogenesis [12]
Various viral proteins with oncogenic properties allow hepatitis C virus to directly induce hepatocellular carcinoma by altering the host's regulatory pathways illustrated above. *ROS (Reactive Oxygen Species).*

Although the exact mechanism through which the HCV core protein induces HCC is still unclear, this protein has shown to be involved in transformation, apoptosis, cell signalling and transcription activation [10]. It is also able to bind to p53, therefore promoting cell proliferation and inhibiting apoptosis [14].

The increase of reactive oxygen species (ROS) during chronic inflammation with HCV can damage hepatocytes, eventually causing cell death and favouring the development of HCC. The consequent liver regeneration favours chromosomal

instability and genetic/epigenetic changes, promoting the proliferation of these transformed malignant cells [12].

Therefore, it is clear that HCV-induced HCC is a result of a combination of the direct effect of HCV on hepatocarcinogenesis and the indirect effect of cirrhosis.

3.3.3. Occult HBV Infection

Some studies have shown that HBV DNA persists in the liver or serum without detectable hepatitis B surface antigen. This situation is known as occult HBV infection, and it has been related to HCC development because its highest rates have been found in those patients with HCC that are alcoholic or have been infected with HCV. In addition, HBx protein is present in the tumour cells of patients with HCC and occult HBV infection. This means that the sole persistence of HBV DNA is an important risk for HCC development, and that the mechanism of hepatocarcinogenesis of occult HBV infection is very similar to that of HBV [10].

4. ONCOLYTIC VIRUSES

The fact that cancer is one of the major diseases that affect the human population makes it necessary to develop therapies that allow us to reduce its high mortality rate. And even though nowadays there are different cancer treatments available, being surgery, chemotherapy and radiotherapy the most representative, these treatments do not always stop metastasis and are incapable of acting specifically on cancerous cells. Moreover, their low therapeutic effects are accompanied by their toxicity to the healthy neighbouring tissues. Therefore, it is clear that a new and highly specific cancer treatment is needed. Targeted cancer therapies would be a more effective approach, since they target tumour cells without affecting the other normal cells [3].

A group of viruses, known as oncolytic viruses (OVs), represent an emerging class of specific cancer therapeutics that can selectively replicate in cancer cells. Although viruses have been used as therapeutic agents in vaccines for a relatively long time, their potential use as cancer therapy was not known until many years later [17].

With advanced biotechnological and genetic methods it is possible to molecular engineer these viruses as targeting elements with higher selectivity and lower toxicity. Viral oncotherapy uses tumour-selective OVs to infect, replicate and kill cancer cells selectively, leaving the surrounding non-malignant cells unharmed and effectively delivering the cancer treatment [3]. In 2005, the adenovirus mutant H101 became the world's first OV approved for cancer treatment [17].

The OVs used in viral oncotherapy can be DNA or RNA viruses that normally are not pathogenic, and that can be either natural tumour selective or genetically-

engineered. One of the benefits of using viral agents as a cancer treatment is that tumour cells lack many natural protection mechanisms against viruses, being highly susceptible to viral infection [3].

The mechanisms used by OVs to kill cancer cells are very diverse, and they range from apoptosis and autophagy to immune response stimulation. They work by infecting malignant cells and replicating within them, killing the cell after that and releasing the resultant viral progeny for further infecting the surrounding cancer cells. In case the specificity fails and the virus infects the normal cells of the tissue in which it was inoculated, the intracellular machinery of said cells will block viral replication, so the non-cancerous cells will be spared (Figure 3) [3].

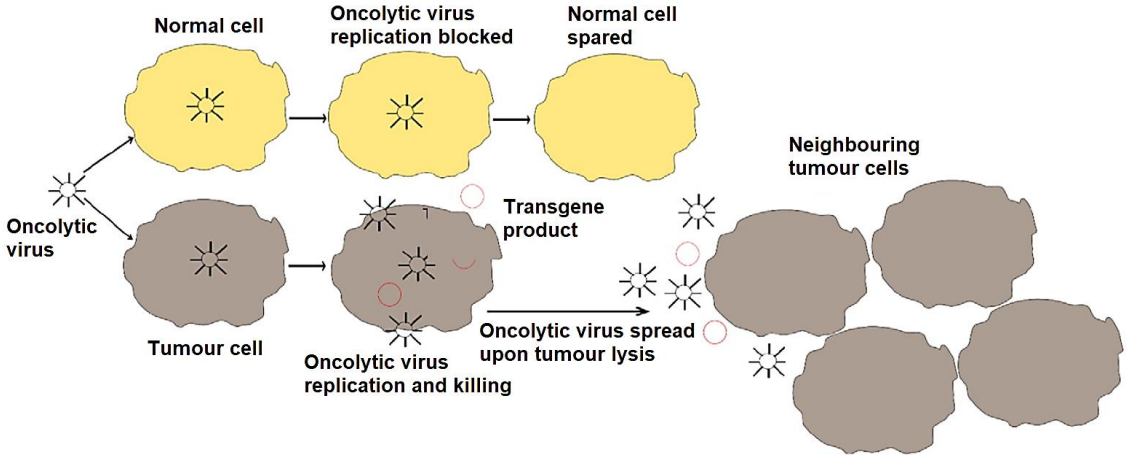

Figure 3: Mechanism of OVs killing tumour cells [3]

Oncolytic viruses specifically detect cancer cells. After infection, OVs replicate within the tumour cell, killing the host when releasing the resultant progeny for further infecting the surrounding cancer cells. When virus-cancer cell specificity fails, normal cells can be infected; viral replication will be blocked by the intracellular machinery of these healthy cells, which will survive the viral infection.

4.1. Mechanisms of Tumour Selectivity

4.1.1. Natural Viral Tropism for Cancer Cells

In nature there are some viruses that show an innate ability to target cancer cells selectively and more efficiently than normal cells. This is because, for infection to occur, viruses are able to selectively bind to certain surface receptors cancer cells express. Viruses also take advantage of the deficient defence mechanisms that characterises cancer cells, which makes them susceptible to viral infection [17].

4.1.2. Enhancing OV Tumour Selectivity

Genetic engineering has enabled the modification of viral genome to increase tumour selectivity. Even though viral gene inactivation is a common strategy [17], it is currently of particular interest using viral vectors in which most of the genome can be replaced with the desired therapeutic gene for its expression at the tumour

cells [3]. Adenoviruses, for example, provide large foreign DNA capacity, low mutagenesis rate and act as efficient delivery agents of therapeutic genes [17].

Moreover, these engineered OVs can also be used to target Cancer Stem Cells (CSCs), which are more resistant to chemo and radiotherapy than normal cancer cells and are able to re-initiate a more aggressive tumour [3].

Viral surface proteins can also be modified to broaden the spectrum of action to different tumour types and to target surface receptors of specific cancer cells with high affinity. Furthermore, cancer cell deaths can also be induced through the introduction of suicide genes in the viral genome, which encode enzymes that are able to intracellularly turn non-toxic metabolites into toxic metabolites. Likewise, immune-stimulating transgenes can be expressed in larger OVs to upgrade their therapeutic effect by inducing the immune response [3]

4.2. Oncolytic Virus-based therapies

Even though clinical studies have demonstrated the efficacy of OVs in cancer treatment, the exact mechanisms are still not completely understood. However, it is clear that viral oncotherapy acts in two different ways: either by killing both virally-infected and non-infected cancer cells or by enhancing the immune response to attack virally-infected cells. Moreover, as most cancers are able to avoid apoptosis, malignant cells can be lysed through non-apoptosis-dependent mechanisms, such as necrosis, autophagy, senescence, etc. [17].

Further research is still needed to exploit the true therapeutic potential of OVs and to overcome the limitations of their use in triggering the immune response against viral vectors. Nevertheless, the great progress made in recent years only confirms the promising future of oncolytic viruses as therapeutic agents in cancer treatment.

4.2.1. Enhancing OV Antitumoural Response

Genetic engineering allows the removal of viral genes to introduce therapeutic genes in order to improve tumour selectivity [17]. In order to maximise their efficacy, OVs can be armed with immune-enhancing cytokines that are capable of intensifying the host's immune system in order to attack cancer cells [18]. One of the most promising cytokines is interleukin-12 (IL-12), which shows strong antitumour qualities and stimulates the innate and adaptive immune responses. It has been reported that the expression of IL-12 in genetically engineered OVs grants the activation of T and NK cells, which participate in the lysis of tumour cells [18].

Viruses that express suicide genes have also been engineered. These genes increase the susceptibility of cancer cells to apoptosis or treatment with other drugs. But the lysis and necrosis of cancer cells can also be achieved when

genes that encode anti-angiogenic molecules are integrated in engineered OVs [17].

Because of its tumour suppressor nature, wild-type p53 is essential in cancer development. However, when mutated it can acquire oncogenic activities, giving cancer cells a selective advantage against normal cells. The fact that nearly 50% of cancers present p53 mutations makes it necessary to develop new approaches to restore the wild-type function of p53. This gene has been introduced in several genetically engineered OVs to increase therapy safety and tumour selectivity and toxicity while promoting the stimulation of antitumour immune response. In addition, if the OV with the p53 transgene infected a normal cell the replication of the virus would be inhibited by the expression of the wild-type p53 endogenous gene [19].

4.2.2. Herpes Simplex Virus

Because of its range of benefits, one of the most widely investigated viruses in cancer therapy is Herpes simplex virus type 1 (HSV-1). This virus can be used as an antitumour agent by replicating in malignant epithelial and neuronal cells, which are its main infection targets [20].

Its growing popularity as an agent in viral oncotherapy is because of its large genome, which can be easily manipulated and in which multiple transgenes can be introduced. HSV-1 is also able to infect a multitude of different types of cancer cells, within which it replicates rapidly, and its genome does not integrate into that of the host. After infection, HSV-1 produces a progeny of viruses that will be released, lysing the host and infecting the surrounding tumour cells [21]. In addition, by using OVs to destroy cancer cells a new source of tumour antigens is obtained, with which antitumour immunity is likely to be further stimulated [20].

As the tumour microenvironment is characterised for its leaky vasculature and absence of functional lymphatic vessels, the most reliable technique to deliver HSV-1 is direct inoculation to multiple tumour sites. This inoculation technique is further supported by the fact that the dispersal of HSV-1 through the circulatory system could be dangerous for cancer patients, as they have supressed systemic immunity [21].

Oncolytic HSV-1 has proved to be a valuable therapeutic agent for controlling different types of cancer. In fact, in 2015, the first oncolytic HSV-1 (T-VEC) was approved by the FDA (US Food and Drug Administration) for the treatment of advanced melanoma [20].

4.2.3. Vaccinia Viruses

Together with HSV-1, the oncolytic Vaccinia Virus (VACV) has been considerably studied. This virus replicates in the host’s cytoplasm after 3 days of infection,

without integrating its viral DNA into the cell's genome. Besides that, oncolytic VACVs can contain multiple large transgenes and move through the bloodstream to target a wide range of distant tumours [22].

Although oncolytic VACVs can be engineered to increase their tumour specificity, they are still vulnerable to be lysed by the immune system of the host. Therefore, it is necessary find new ways of protecting oncolytic viruses from the host's immune response. One option is the administration of immunosuppressive drugs while using carrier cells, which are immune or tumour cells used to ensure the delivery of OVs to tumours and to protect them from inactivation by neutralizing antibodies. However, the use of cancer cells as delivery vehicles is concerning, so new strategies are being proposed [22].

Cytokine induced killer (CIK) cells can be used as carrier cells, as they are able to target selectively a wide range of tumour cells and they do not show VACV antigens on their surface. When they bind to their tumour receptor, CIK cells undergo lysis, introducing the OVs into the tumour cells [22].

Due to the large size of VACVs, the main pathway for cell entry seems to be endocytosis. This is a favourable aspect, since endocytic vesicles protect the viruses from circulating antibodies and, in addition, their presence in the cell is not reflected on the exterior of the plasma membrane [22].

Therefore, oncolytic VACVs seem to be effective agents in viral oncotherapy, as they act over a broad spectrum of cancer cells, can be delivered without being noticed by the immune system and allow the introduction of large genes into their genome in order to increase their selectivity.

4.2.4. Tumour-associated Macrophages in Oncolytic Virotherapy

Oncolytic viruses do not only destroy tumours directly, that is, through infecting and lysing cancer cells, but they can also activate the host's anti-tumour immune response. The tumour-associated macrophage population is essential in cancer immunotherapy, but they can also participate in oncolytic virotherapy [23].

While further research on this subject has yet to be carried out, it is known that although M1-like macrophages promote the anti-viral immune response, they can also enhance the virus-mediated activation of the anti-tumour immune response. Moreover, the inflammatory macrophages can also produce certain metabolites with anti-angiogenic effects and improve OVs response in some tumours [23].

4.2.5. Viral Oncotherapy in Hepatocellular Carcinoma

As it was mentioned before, hepatocellular carcinoma (HCC) is one of the most common types of cancer. However, the current treatments for HCC have a lot of

limitations and do not guarantee survival. This is what makes HCC attractive for viral oncotherapy and immunotherapy [24].

The most used viruses in HCC treatment have been oncolytic adenovirus and vaccinia virus. These OVs were genetically engineered to selectively infect HCC cells and express genes that allow the recruitment of circulating neutrophils, monocytes and lymphocytes in the surrounding blood vessels, improving their function on host defence. Therefore, by combining the action of oncolytic viruses with the cells of the immune system, HCC treatment could be stimulated [24].

4.3. Combination of Therapies

Surgery, chemotherapy and radiotherapy are still the most used therapeutic approaches to cancer. And although they provide immediate treatment of cancer cells, their efficacy is fairly limited. They do not always completely block cancer growth and metastasis, enabling the potential growth of cancer cells with higher drug resistance, and they can sometimes affect normal cells [25]. However, it has been reported that combining oncolytic viruses with these three therapies can help increase the response obtained with each therapy alone [26].

OVs benefit from some chemotherapeutic agents, as they upregulate some of the cell surface receptors that viruses use to enter and infect cancer cells [27]. Other drugs affect the immune response, therefore enhancing OV function [28].

Antitumour response is also improved by the combination of oncolytic virotherapy with radiation. There are OVs that have been engineered so that they express therapeutic genes that enhance local radioactive particle delivery of iodine [29].

5. CONCLUSION

Cancer is one of the major diseases in today's world, as it affects a large ratio of the human population. Certain animal viruses, the so-called oncogenic viruses, can trigger carcinogenesis in humans through very different ways. Some of the most important oncogenic viruses are human papillomavirus (HPV), Epstein-Barr virus (EBV), hepatitis B virus (HBV) and hepatitis C virus (HCV). Their presence in the human population depends on the geographical location, and the chances of developing cancer depend on the virus itself and the patient's environment. However, the significant influence of these viruses in carcinogenesis makes it necessary to understand the mechanisms by which these agents induce tumour development. It is also important to know the molecular machinery implied in this process of carcinogenesis, so that it can be used therapeutic targets.

Other viruses can selectively target cancer cells, replicating within them and killing their host when the resultant viral progeny is released to further infect the surrounding tumour cells. Advanced biotechnological and molecular methods have made it possible to genetically engineer these viruses, deleting pathogenic

genes and introducing therapeutic genes into the viral genome. Some of the most promising oncolytic viruses are herpes simplex virus type 1 (HSV-1) and vaccinia viruses (VACV). Based on encouraging evidence over the safety and efficacy of these oncolytic viruses, and along with the fact that when combined with traditional cancer treatments they increase the efficacy of chemotherapy and radiotherapy, it is clear that viruses may become a new modality for the treatment of cancer.

CONCLUSIÓN

El cáncer es una de las enfermedades más importantes en la sociedad actual, ya que afecta a un gran porcentaje de la población humana. Ciertos virus animales, los denominados virus oncogénicos, son capaces de desencadenar la carcinogénesis en humanos por medio de vías muy distintas. Algunos de los virus oncogénicos más importantes son el virus del papiloma humano (VPH), el virus Epstein-Barr (VEB), el virus de la hepatitis B (VHB) y el virus de la hepatitis C (VHC). Su presencia en la población humana depende en la localización geográfica, y las probabilidades de desarrollar un cáncer dependen del propio virus y del ambiente del paciente. Sin embargo, la importante influencia que estos virus tienen sobre la carcinogénesis hace que sea necesario comprender los mecanismos por los que inducen el desarrollo de tumores. También es necesario conocer la maquinaria molecular implicada en estos procesos, para que pueda ser utilizada como diana en nuevas terapias.

Otros virus pueden detectar selectivamente células cancerosas, multiplicándose en su interior y matando a su huésped cuando la progenie viral resultante es liberada para infectar a las células tumorales circundantes. Los avances en los métodos biotecnológicos y moleculares han permitido someter a estos virus a ingeniería genética, introduciendo genes terapéuticos y eliminando genes patógenos. Algunos de los virus oncolíticos más prometedores son el herpes simple tipo 1 (VHS-1) y el virus vacuna (VACV). Distintos estudios han aportado evidencias alentadoras sobre la seguridad y la eficacia de estos virus oncolíticos, y junto al incremento que se observa en la eficacia de la quimioterapia y la radioterapia cuando se combinan con ellos, es evidente que los virus pueden llegar a convertirse en una nueva modalidad de tratamiento contra el cáncer.

CONCLUSIÓNS

O cancro é unha das enfermidades máis importantes da sociedade actual, xa que afecta a unha gran porcentaxe da poboación humana. Certos virus animais, chamados virus oncoxénicos, son capaces de desencadear carcinoxénese en humanos por diferentes rutas. Algúns dos virus oncoxénicos máis importantes son o virus do papiloma humano (HPV), o virus de Epstein-Barr (EBV), o virus da hepatite B (HBV) e o virus da hepatite C (HCV). A súa presenza na poboación humana depende da localización xeográfica, e as posibilidades de desenvolver

cancro dependen do propio virus e ambiente do paciente. Con todo, a importante influenza que estes virus teñen na carcinoxénese fai necesario comprender os mecanismos que inducen o desenvolvemento dos tumores. Tamén é necesario coñecer os mecanismos moleculares implicados nestes procesos, para que poidan ser utilizados como diana en novas terapias.

Outros virus poden detectar selectivamente as células cancerosas, multiplicarse no seu interior e matar ó seu hospede cando a descendencia viral resultante é liberada para infectar as células tumorais veciñas. Os avances na biotecnoloxía e nos métodos moleculares permitiron someter estes virus a enxeñaría xenética, eliminando xenes patóxenos e introducindo xenes terapéuticos. Algúns dos virus oncolíticos máis prometedores son virus vaccinia (VACV) e herpes símplex tipo 1 (HSV-1). Varios estudos aportaron evidencias alentadores sobre a seguridade e eficacia destes virus oncolíticos, que xunto coa mellora observada na eficacia da quimioterapia e radioterapia cando se combinan con eles, queda claro que os virus pode ser un nova forma de tratamento do cancro.

6. REFERENCES

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