Transmissible tumors: by what mechanisms do they act?

Usually, we tend to attribute the cause of cancer to genetic factors with a "birth, development, action" process directly derived from uncontrolled mutations of the same cells in the affected organism, limited therefore to the individual; however, there are also cases that can be defined as "transmissible". Although there is no clear and established definition of "transmissible tumor", it generally refers to a neoplasm that can propagate from an affected individual to another individual (usually of the same species) through different transmission mechanisms, such as "inoculation" of cells containing oncogenes that resist the host's immune system, or infection with viruses that can lead to a tumor-like cellular stage. These are relatively new diseases for medicine, but how do they differ from autogenous tumors and what are the mechanisms involved in this process? Firstly, it should be noted that (to date) such neoplasms have not been observed as an endemic phenomenon in primates, let alone in humans: for academic purposes, there are very rare cases, such as a malignant fibrous histiocytoma transmitted from a patient to a surgeon by injuring the hand during surgery (a 1996 study showed that the two tumors were genetically identical), or an equally suspicious transmission of cancer cells from a mother with oncological pathology to her fetus. Based on these cases, it is presumed that a neoplasm can, under exceptional conditions, also migrate in humans. However, these are currently considered unique situations, so the risk of "occasional" direct human-to-human tumor transmission is certainly negligible. On the other hand, the same cannot be said for other animal species: in fact, although still a rare occurrence, symptoms have been detected that have led to the identification of transmissible neoplasias in species such as canids, some felines, Cheloniae (marine turtles), deer, and Sarcophilus harrisii (the so-called "Tasmanian Devil"). However, the cause of transmissible tumors varies from species to species: for example, canine transmissible venereal tumor is transmitted through sexual contact, while the facial tumor of Tasmanian devils spreads through direct physical contact. In all these cases, scientific research has divided such pathologies into two groups: - The cancer-transmitting agent is made up of tumor cells that are able to "migrate" from one animal to another. The disease transmission can then be defined directly, i.e., an "ill" individual transfers tumor cells to another during a contact. - The tumor-transmitting agent is made up of a virus, which, for multiple reasons, is able to induce degenerative conditions in the cells it is in contact with. In this case, indirect transmission can be mentioned, i.e., the "infected" individual does not transmit the disease itself but only the pathogenic agent which, however, determines an oncological course. This differentiation is due to the substantially different mechanisms of action. As a scientific interest, the most studied cases have been those of canids and Sarcophilus harrisii because they belong to the category of migratory cancer cells.

The “Canine Transmissive Veneral Tumor” in canids:

In canids, CTVT can affect all subspecies, including foxes, coyotes, licaons, dingoes, wolves, and other wild canines, as well as domestic dogs. In fact, one of the theories regarding its origin suggests that this disease was originally transmitted from a common ancestor of canids and then evolved differently in each species through changing environmental conditions, such as geographical habitat, population density, and pack interaction. However, domestic dogs are believed to be more frequently exposed to CTVT than wild canines due to their close contact with other dogs and reproductive practices. CTVT is a direct transmissible tumor caused by a single tumor cell line, characterized by genetic mutations that make it resistant to both the original organism's immune system and the infected host. As a unique cell line, we refer to a population of tumor cells that derive from a single original cell, i.e., the progenitor cell that has spread through sexual contact with an infected dog. CTVT cells are morphologically identical and share the same genetic traits, as they all originated from a single malignant cell. Among the genes involved with CTVT, the MHC gene (Major Histocompatibility Complex) has been identified, which regulates the dog's immune response against tumor cells. The fact that CTVT tumors are able to elude the host's immune response suggests that these tumor cells might be able to suppress the immune system's activity, leaving the tumor mass free to proliferate. In addition, it has been discovered that CTVT tumors have a higher expression of genes involved in cell proliferation, such as the cyclin-dependent kinase inhibitor 2A (CDKN2A) gene. This increased activation of proliferation genes could be responsible for the high growth capacity of CTVT tumors. There is also a specific mutation in the PDGFR-α (Platelet-Derived Growth Factor Receptor alpha) gene, known to regulate cell growth and differentiation. This mutation could be responsible for the development of such neoplasia in tissues involved in sexual activity, or genital organs, since the PDGFR-α receptor is specifically active in these areas. Based on all this information, the disease is therefore transmitted sexually through body fluids that incorporate this mutation and are able to avoid the immune system, transferring to the host and continuing their reproduction. However, the specific involvement of these genes in CTVT progression is not yet fully understood and requires further study. At a pathological level, it is usually a benign tumor, i.e., it does not present metastases and rarely spreads to other parts of the dog's body. The symptoms of CTVT include the appearance of nodules in the dog's genital area, which can become larger over time. Although CTVT is a condition that can cause concern and nodules can become painful, bleed, or cause urination or defecation problems. The neoplasm can be successfully treated with chemotherapy or surgical removal of the tumor, resulting in a generally good prognosis, with a healing rate close to 90% without recurrence. However, it is important to adopt a system of control of the animal's habits in its interaction with its peers, aimed at preventing the occurrence of new risky situations that can bring back the pathology. To date, no vaccine has been developed, also considering the effectiveness that surgical and chemotherapy treatments offer.

The “Devil Facial Tumour Disease” in Sarcophili Harrisii:

Another known case of direct transmissible tumor is that of the facial tumor (DFTD) of the Sarcophilus harrisii, or Tasmanian devil. This marsupial, native to Tasmania, has undergone a sharp demographic decline due to this disease. In particular, DFTD affects the soft tissue of the face, through the proliferation of an aggressive neoplasm that mechanically prevents the animal from feeding, to the point that death often becomes inevitable. Also in this case, it is caused by a single tumor cell line that replicates within the host's organism: in particular, it is characterized by a mutated gene region, which has been identified in the modification of the "TP53" gene, which allows tumor cells to survive despite the immune response of the host individual, thus preventing their destruction. Specifically, the "TP53" gene encodes for a protein known as p53, which in many organisms promotes programmed cell death (known as apoptosis). It is believed that the absence of this protein makes the cells more resistant to death, no longer eliminating damaged ones in the organism: this absence therefore compromises the immune system's ability to detect and destroy tumor cells, allowing them to spread throughout the body and be transmitted to other members of the colony. According to current data, it is possible that the absence of the p53 protein may also alter the expression of other genes involved in regulating cell division and death, thus promoting tumor proliferation, but studies in this regard are still ongoing. Unlike CTVT, the mutation allows diseased cells to continue to replicate and spread, contributing to the progression of cancer to the point that DFTD has become an endemic disease of the Tasmanian devil species, reducing its population by 90%. Recently, an experimental vaccine has been developed by a research team at the University of Tasmania in Australia. This procedure uses an adenovirus as a vector in which the specific viral sequence has been added. The vaccine has been tested in the laboratory on tumor cells and some animals. According to scientists, the vaccine has been shown to activate the animals' immune system and make tumor cells vulnerable to their attack. Obviously, we are still in the early stages, and it will take years to evaluate its effectiveness both in the short and long term.

The Feline Leukemia Virus in felines:

The Feline Tumor Virus, which causes neoplasia in felines, has been identified in three species of wild felines: the Jungle cat, the lion and the jaguar. This causes tissue alteration and the subsequent uncontrolled proliferation of such tumor cells. The virus is mainly transmitted through direct salivary contact, but can also be transmitted through mother's milk and infected blood. The tumor pathology has been attributed to mutations in some important cellular proteins that regulate the cell division process. For example, in jungle cats, it has been associated with the aforementioned mutation in the "TP53" gene, involved in apoptosis and DNA repair processes (similarly to what happens to Tasmanian devils). This mutation also causes an increased susceptibility to carcinogens. In jaguars, it has been associated with a

mutation in the TMEM154 gene that encodes for a protein involved in modulating the immune response. This mutation causes a compromise of the immune system that increases the susceptibility to neoplasm formation. In the long term, this clinical condition can cause various pathologies, including the formation of tumors in the central nervous system, gastrointestinal tract, lymph nodes, and skin. Moreover, the condition can be asymptomatic for a long time, making the specific diagnosis sometimes difficult. On a prognostic level, there is a vaccine available for the Feline Leukemia Virus (FeLV). The vaccine can be administered starting from 8 weeks of age and requires an initial two-dose cycle spaced three or four weeks apart. After the initial cycle, felines must be revaccinated every year to maintain immunity. However, the vaccine is not 100% effective in preventing infection and transmission of the virus. Some specimens can still contract FeLV despite vaccination, but the infection tends to be less severe in these cases.

The "Turtle Tumor-Associated Virus - Chelonid herpesvirus 5" in turtles:

Chelonid herpesvirus 5 is a virus that causes tumors in the skin and soft tissues of sea turtles. Although studies are still ongoing, ChHV5 appears to act through the activation of a series of oncogenes, such as the v-myc avian myelocytomatosis viral oncogene homolog (MYC) gene, the FGFRL1 growth factor gene, and the N-myc downstream-regulated 1 (NDRG1) gene. These can in turn interact with other transcription factors to regulate the cell life cycle and contribute to tumor growth. This virus is transmitted through direct contact between turtles and can cause tumors on the skin, eyes, fins, and other internal organs of sea turtles, which are then spread to other specimens. The infection infiltrates the immune system cells of turtles, where it replicates and causes damage to healthy tissues, compromising the immune system itself and promoting the proliferation of tumor cells in the organism. In addition, the virus can become latent inside cells and reactivate later in times of stress or when the immune system is weak, causing recurrences. The disease has been observed mainly in green turtles (Chelonia mydas), but can also occur in other sea turtles such as hawksbill turtles (Eretmochelys imbricata), and less commonly in loggerhead turtles (Caretta caretta, also present in the Mediterranean), among other species. The tumors caused by the ChHV5 virus are generally highly aggressive and can spread rapidly throughout the animal's body. This leads to a reduced ability to feed and move properly, increasing the risk of infections and other complications. Therefore, the prognosis for an animal affected by ChHV5 is not very favorable and in the absence of supportive therapy that ensures proper nutrition and hygiene, life expectancy is limited. Currently, there is no vaccine available to prevent ChHV5 infection, as it is a very complex and mutable virus. As an academic issue, the virus genome has been sequenced and is composed of a circular double-stranded DNA molecule containing about 200,000 base pairs. The possibility of developing a vaccine still seems far off, although researchers are actively working to fully understand all the functioning and activation processes of the virus itself.

The "Chronic Wasting Disease" in deers:

The Chronic Wasting Disease (CWD) is caused by an anomalous prion, a pathogenic protein present in deer cells. In particular, this protein is an altered conformation of the endogenous prion protein (PrP) of the deer. A PrP is a type of cellular protein found in most mammalian tissues and plays an important role in the physiology of the central nervous system. It is produced by the cells of the body in a "protected" form and usually does not cause any problems. However, in some rare cases, a mutation or anomaly occurs, altering its conformation, called abnormal prion protein or PrPSc. The mutated form integrates the property of self-aggregation and resistance to normal cellular defenses. When it comes into contact with its counterpart in the unmodified form, the anomalous protein induces a conformational change that, in turn, leads to the formation of abnormal and harmful protein aggregates for the nervous system. The presence of abnormal prion proteins is associated with the onset of numerous neurodegenerative pathologies, causing even extensive brain lesions. Transmission occurs through direct contact with infected specimens during mating, fighting during the breeding season, or foraging. The disease can be transmitted through bodily fluids such as saliva, feces, and urine, which can contaminate the soil and water, promoting its spread. CWD can also be transmitted through the consumption of contaminated grass or plants. It is also suspected that CWD transmission may occur indirectly through vectors such as mosquitoes, flies, fleas, and other parasites. The disease can spread rapidly in wild deer populations, with sustained transmission that can persist for years even in the absence of confirmed cases. There is currently no therapy or cure, as the abnormal proteins that cause the disease do not respond to normal pharmacological treatments. The prognosis for animals infected with CWD is generally unfavorable, as the disease progresses slowly but inevitably leading to the death of the animal. Symptoms of the disease may include weight loss, decreased appetite, abnormal behavior, difficulty in walking, tremors, and other neurological problems. Animals affected by CWD generally die within one or two years of infection. Currently, there is no vaccine to prevent transmissible deer disease or other prion diseases, leaving prevention as the only useful strategy for the spread of the disease. This is mainly based on surveillance of deer populations and the implementation of biosecurity measures, such as the elimination of infected individuals and the decontamination of at-risk soil.

Differences and similarities between autogenous and transmissible tumors:

At this point, we can draw more detailed comparisons between these two types of tumors: Autogenous tumors are the result of genetic mutations in the cells of the affected organ or tissue. Transmissible tumors, on the other hand, are mostly tumor tissues that are transmitted from one individual to another. Despite the evident differences in their etiology, autogenous and transmissible tumors have some similarities, especially regarding their pathophysiology and effects on the cells or tissues of the organism. Firstly, both are characterized by uncontrolled

cell growth, with the fundamental difference being that autogenous tumors originate from within the affected organism due to genetic or epigenetic mutations that alter cell growth and differentiation. On the other hand, in transmissible tumors, the neoplastic mass is "delivered" already mutated from a carrier individual to another.

Analogies: In all types of neoplasms, mutations can be caused by internal factors such as ethnicity, age, gender of the individual, and their own genome, or external factors such as exposure to ionizing radiation, toxic substances, or environmental pollution. These factors damage the DNA of cells, causing genetic mutations that, in some cases, can lead to tumor formation. Uncontrolled cell growth can result in the compression or destruction of neighboring tissues and organs, as well as the further spread of tumor cells, with the possibility of chronic inflammation in the affected areas or in the entire affected organism, as well as the development of adaptation and resistance to antibodies. Inflammation is a natural response of the body to lesions, infections, or (in oncological cases) in response to tissues recognized as "incompatible" (such as those consisting of non-host tumor cells), but if it becomes chronic, it can create an environment favorable to the proliferation of altered cells themselves. Tumors in general can trigger constant inflammation by producing pro-inflammatory substances such as cytokines, which activate the immune system: specifically, cytokines are protein molecules produced by the immune system in response to inflammation or infection. They have a communicative role between the cells of the immune system and are involved in many body functions, including activation of white blood cells and regulation of the immune response against inflammation. There are several types of cytokines, including interleukin (IL), tumor necrosis factor (TNF), interferon (IFN), and chemokine (CXCL). Each of them has a specific role in coordinating the immune response. Cytokines can be produced by different types of cells, including macrophages, dendritic cells, T and B lymphocytes, and different types of stromal cells, effectively regulating the entire immune system to eliminate the pathogen or damaged tissue. However, even excess cytokines can cause damage to the organism: excessive production can damage the surrounding healthy tissues and lead to autoimmune diseases (such as rheumatoid arthritis or Crohn's disease).

Differences: The main difference concerns the genesis of the tumor and the nature of the causative agent. Transmissible tumors are generally caused by the uncontrolled cell proliferation of something external (analogously to what happens with viruses, bacteria, or parasites). As mentioned before, the dividing line is blurred if compared to other "infectious" processes, since the behavior is similar, i.e., since the non-compatible proteins with the host's genetic sequence enters; they are attacked by the immune system like any other foreign biological entity, in some cases triggering an excessive and harmful immune response, or inhibiting the immune response itself due to their nature. In all these cases, when an immune response is ineffective, it fails to eliminate the pathogen (viral or tumor) which leads to its continued reproduction and propagation wherever it can. This fundamental difference is

important for understanding that it is not the genetic sequence of the target organism that is at risk, but the effects of the propagation that this foreign body has on the tissues or organs with which it interacts.

Treatments in these types of diseases:

Due to the diversity of tumor formation and the fact that they:

- are not derived from the animal's genetic heritage but from "parasitic" tumor cells imported from the outside;
- are sometimes caused by viruses that cause tumor stages, for which a different approach from traditional oncology is needed;
- transmission occurs through physical contact between animals, as naturally occurs in all of the aforementioned species, causing the subject at risk to fall into an endless cycle, even if cured with the help of external therapies, remaining constantly at risk for new relapses, since it is not able to independently eradicate the disease;

Scientific research has therefore focused on other strategies that aim to strengthen the immune system of affected subjects or to correct deficits caused by any altered genes in the tumor itself. For example, in the case of DFTD in Tasmanian devils, the p53 protein has been used, as previously mentioned, which is often inactivated in this pathological framework. It has been hypothesized that the use of this protein could stimulate the immune system to recognize and destroy tumor cells. Another research strategy has been to use the so-called "immunological transplant," i.e., the transplantation of immune cells from animals resistant to transmissible tumors to those who are sick. However, this technique presents problems related to tissue compatibility and the ability of donor cells to completely eliminate the host's tumor cells. The vaccine road is achievable, like was done for the FeLV, but not without obstacles, such as the Tasmanian devil case. In conclusion, there is currently no definitive evidence that these approaches will lead to the desired results. This is also due to the fact that these are relatively new discoveries, dating back only a few decades, placing them on a relatively new biological and pharmaceutical level.

Bibliography:

- Hannah V Siddle, Jim Kaufman: "Tumour transmission studies reveal mechanisms of immunoevasion in Tasmanian devils and HLA diversity in humans"
- Chand Khanna: "Cancer in Dogs, Cats, and Domestic Animals: New Advances in Detection and Treatment"
- Murgia C, Pritchard JK, Kim SY, Fassati A, Weiss RA: “Clonal origin and evolution of a transmissible cancer”
- Katherine Belov: "Contagious cancer: lessons from the devil and the dog"

- Torres AN, Girard N, Tandon R: “Feline leukemia virus infection and associated diseases”
- Michael J. Metzger, Carol Reinisch, James Sherry, Stephen P. Goff: “Horizontal Transmission of Clonal Cancer Cells Causes Leukemia in Soft-Shell Clams"
- Stöhr, A.C., López-Bueno, A., Blahak, S., Caeiro, M.F., Rosa, G.M., Alves de Matos, A.P., Gjessing, M.C., Christoffersen, M., Alejo, A., & Marschang: “Phylogeny and differentiation of reptilian and amphibian alphaherpesviruses and comparison of their glycoprotein B to those of mammalian herpesviruses”
- Detwiler, L. A., Baylis, M., Greenlee, J.: “The epidemiology of chronic wasting disease: a brief overview and implications for wildlife and livestock”
- US Department of Agriculture (USDA): “Chronic Wasting Disease: A guide to hunters in the containment zone. Animal and Plant Health Inspection Service”

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