

Oncogenic Microbes and Their Role in Cancer

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Learning Objectives (3)

After completing this brick, you will be able to:

- 1 Describe the mechanisms by which oncogenic microorganisms cause cancer.
- 2 List the main cancers associated with oncogenic microorganisms.
- 3 List the main types of oncogenic microorganisms and describe the cell affinities for each.

CASE CONNECTION

You are seeing RS, a 32-year-old male, in the dermatology clinic during a fourth-year elective. You note multiple, red-violet, raised lesions on his arms. "That's what I'm here for," RS says. "They continue to grow." RS has had no new contacts or exposures. He is receiving antiretroviral therapy for HIV infection. His exam is otherwise unremarkable.

What is the diagnosis? Consider your answer as you read, and we'll revisit RS at the end of the brick.

[GO TO CONCLUSION](#) 

Did you know that some cancers are caused by microorganisms such as viruses, bacteria, and parasites? Viruses are especially well known for causing cancers like [cervical cancer](#), [B-cell lymphomas](#), and [hepatocellular carcinoma](#). In this brick, we will take a look at nine microorganisms, which cells they target, their mechanisms of action, and what cancers they can cause.

INSTRUCTOR NOTE

There are a lot of details in this brick that are not required at this point. The important take away is to know which viruses, bacteria, etc. are associated with which cancers. Details will follow in other future sessions.

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Viruses: The Front Runner

That common cold you have had for the last 2 weeks because you were too tired to go to the doctor? Watch out! Just kidding—sort of. The common cold probably will not cause cancer, but 12% of cancers are caused by viruses. Viruses typically target specific cell types. They take over the machinery of the cells and can alter genes. When this occurs, the cell can be turned toward the path of cancer. Let's take a look at a few of the most common oncoviruses (ie, viruses that cause cancer).

Epstein-Barr Virus

Epstein-Barr virus (EBV), also called human herpesvirus 4 (HHV-4), is best known as the cause of mononucleosis or “mono.” Mononucleosis is often referred to as the “kissing disease” because it is most commonly transmitted by salivary contact during the teenage years. Although mononucleosis itself does not cause cancer, EBV can lead to its development.

How does this happen? EBV targets B lymphocytes. It often remains latent in these cells for a very long time, binding to the CD21 cell marker. With the affinity for this cell type, this virus is more likely to infect these cells and alter their genetic make-up. This action increases the chances for two types of cancers that are associated with B cells: Hodgkin lymphoma and Burkitt lymphoma.

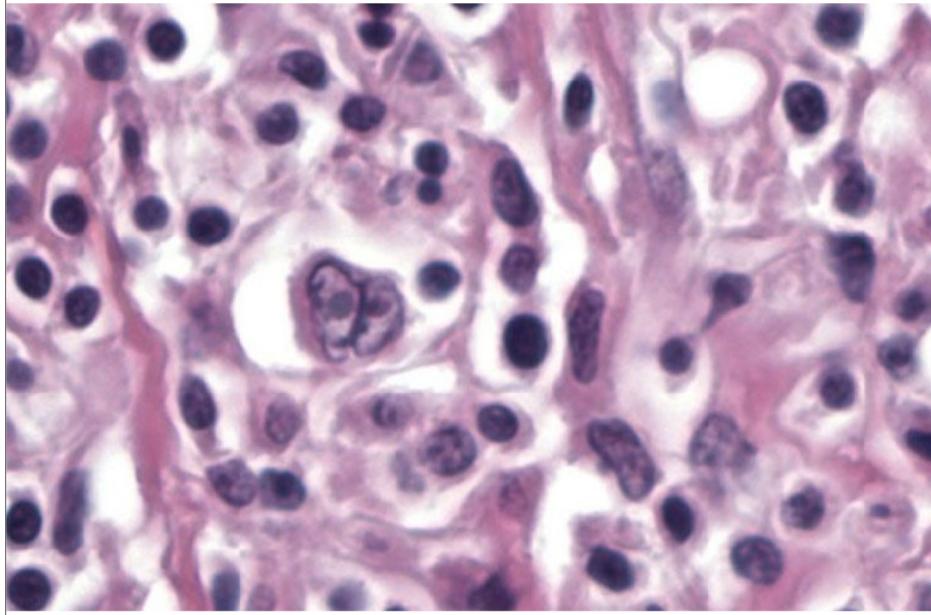
Which cancers are associated with EBV infections?

Hodgkin lymphoma cases are related to infection with EBV about 50% of the time. Risk factors for developing Hodgkin lymphoma include immunosuppression and a family history of the disease. On histology, this cancer is typified by the presence of Reed-Sternberg cells, colloquially referred to as “owl eye” cells because they typically have a bilobed nucleus with prominent eosinophilic inclusion-like nucleoli ([Figure 1](#)).

INSTRUCTOR NOTE

We will discuss this further in Lymphomas. For now just know the association between EBV and Hodgkin Lymphoma and Burkitt lymphoma

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QUIZ

Tap image for quiz

Figure 1

CLINICAL CORRELATION

An important difference between Hodgkin and non-Hodgkin lymphoma on light microscopy, which can be seen in [Figure 1](#) with an H&E (hematoxylin and eosin) stain, is the presence of Reed-Sternberg cells in the former condition.

Burkitt lymphoma is a type of [non-Hodgkin lymphoma](#). About 75% of cases have a t(8;14) translocation, resulting in translocation of c-MYC and [immunoglobulin heavy-chain locus](#) (IgH), which causes increased constitutive levels of c-MYC. c-MYC signaling helps the cancer cells survive and proliferate. Under a light microscope, neoplastic B lymphocytes of Burkitt lymphoma appear monomorphic and highly mitotically active.

LECTUROR NOTE

This will be discussed at a later session. The details of Burkitt lymphoma are not necessary at this point.

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There are three subtypes of Burkitt lymphoma:

- African (endemic) Burkitt lymphoma
- Sporadic (nonendemic) Burkitt lymphoma
- Burkitt lymphoma occurring in patients with [HIV](#) infection

The African subtype is, as the name suggests, endemic to certain parts of Africa. It is virtually always positive for EBV and typically presents in children or young adults as a large mandibular mass ([Figure 2](#)). The sporadic subtype also occurs mainly in children and typically presents with a fast-growing mass involving the ileocecum. EBV is found in only 15% of sporadic cases and 25% of HIV-associated cases.

the regulation of vascular endothelial growth factor, or VEGF. VEGF is primarily involved in angiogenesis, the formation of new blood vessels from preexisting blood vessels. The virus allows for VEGF to activate continuously, resulting in increased angiogenesis. This activity is the cause of the red- and violet-colored lesions characteristic of the disease. The cells that HHV-8 targets for this process are primitive mesenchymal cells. Oncogenesis in mesenchymal cells results in a sarcoma instead of a carcinoma (which originates in epithelial cells). HHV-8 also has some affinity for B cells.

This cancer often afflicts immunosuppressed individuals, especially patients with AIDS. Kaposi sarcoma typically presents as red- and violet-colored lesions on the skin of the extremities (Figure 3).

Figure 2

EBV can also cause nasopharyngeal carcinoma. In this case, epithelial cells are the primary target. EBV-associated nasopharyngeal carcinoma is common among adults in Asia and children in Africa. This malignancy resembles squamous cell carcinoma.

Human Herpes Virus 8

Human herpes virus 8 (HHV-8), also known as Kaposi sarcoma–associated herpesvirus, is a herpes virus transmitted by salivary contact. HHV-8 alters

Figure 3

In addition to Kaposi sarcoma, HHV-8 is the cause of a B-cell lymphoma known as primary effusion lymphoma. Primary effusion lymphoma is a rare non-Hodgkin lymphoma. HHV-8 is also positive in multicentric Castleman disease and some cases of multiple myeloma.

Hepatitis Viruses

Hepatitis viruses, specifically hepatitis C (HCV) and hepatitis B (HBV), can cause hepatocellular carcinoma. In both cases, chronic infection results in cirrhosis (ie, fibrosis or scarring in the liver). A significant number of patients with cirrhosis will eventually develop hepatocellular carcinoma. We'll look at each of these viruses individually.

Hepatitis C virus (HCV) is transmitted commonly by IV drug use and occupational exposure, such as a needle stick injury. It is uncommonly transmitted by sex and transplacentally. In the past, HCV was not uncommonly transmitted through blood transfusion or organ transplantation. However, improved screening methods have drastically reduced the incidence of transfusion or transplant-related HCV infection.

The infection causes inflammation of the liver and results in jaundice. About 60%-80% of HCV infections become chronic, which, if you recall, is where the problem begins. The chronic infection causes lymphocytes to accumulate in the liver tissue (this is called hepatitis). Some cases of hepatitis evolve into cirrhosis and eventually into hepatocellular carcinoma (Figure 4).

QUIZ

 Tap image for quiz

Figure 4

Hepatitis B virus (HBV) is transmitted sexually, through IV drug use, and from mother to child during childbirth. Professionals with an increased risk of being exposed to blood with HBV (eg, health professionals, especially nurses and doctors) are required to get the HBV vaccine. The development of hepatocellular carcinoma from chronic HBV infection has the same pathophysiology as HCV. However, it has another key component. HBV can incorporate some of its DNA into the DNA of a host hepatocyte. This allows the virus to perpetuate, leading to a chronic infection. These changes can cause the development of hepatocellular carcinoma over 11

changes can cause the development of hepatocellular carcinoma as well.

Human Papillomavirus

Did you have to get the Gardasil shot when you were a teenager? Both females and males ages 9-26 years can receive this shot to “guard” against human papillomavirus (HPV). HPV is a virus that can cause warts and cancer. It comes in several serotypes. HPV serotypes 1 and 4 cause warts in children, known as verruca vulgaris. HPV-6 and HPV-11 can present as genital warts or recurrent respiratory papillomatosis (skin surface elevations in the larynx).

Several HPV serotypes—most notably HPV-16, -18, -31, and -33—are considered “high-risk” serotypes because they frequently are associated with specific types of cancer, most notably cervical carcinoma, but also certain cancers of the vagina, vulva, penis, anus, rectum, and oropharynx. Let’s take a look at how these strains cause this type of cancer.

The key players affected by HPV are the tumor suppressor proteins p53 and Rb (Rb is the retinoblastoma protein encoded by the RB gene). p53 and Rb are crucial regulators of the cell cycle, specifically the transition from the G1 phase to the S phase. G1 is the phase where most of the cell and its components double in size, except for DNA. S is the phase where the DNA “doubles” or a second set is synthesized from the original strands. p53 and Rb inhibit the progression of the cell cycle from the G1 to S phase.

Arresting this process gives the cell time to correct any issues in duplication of cellular components and any problems found in the DNA before the DNA is synthesized in the S phase. HPV stops this process.

How does HPV stop these tumor suppressor genes from performing their function? HPV encodes for two molecules: E6 and E7. E6 has an affinity for and destroys p53. E7 does the same but with Rb. When p53 and Rb are

destroyed, the cell cycle can continue without any checks from the G1 to S phase. This event permits the multiplication of cells with mutations. These mutated cells eventually become cancer.

INSTRUCTOR NOTE

This will be discussed in Female Reproductive Pathology, year 2. Details are not necessary now except to know that HPV (especially types 16 and 18) is associated with squamous cell carcinoma of the cervix, as well as other types of squamous cell carcinomas to be discussed in the future.

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What is the mechanism of oncogenesis in HPV infection?

Human T-Cell Leukemia Virus Type 1

Human T-cell leukemia virus type 1 (HTLV-1) is a retrovirus like HIV. The virus is transmitted from mother at birth (most common), sexually, and through IV drug use, direct blood-blood contact, and breast milk. The exposure can occur several decades before clinical features appear.

Infection with HTLV-1 primarily affects the CD4 T cells. HTLV-1 produces several proteins that cause changes in the body; the main focus of this discussion is the Tax oncoprotein. The name Tax (transactivator from the X-gene region) comes from the fact that the gene is located on the pX region of the viral *ENV* gene and is an activator of viral protein transcription.

The Tax oncoprotein stimulates new leukocyte production by increasing molecular signaling (IL-2 and IL-15), which promotes T-cell production. In addition, Tax immortalizes T lymphocytes *in vitro* (ie, T lymphocytes that would typically not proliferate indefinitely are now mutated to continue division). Increased proliferation due to Tax protein activity and immune system response can overwhelm the checks and balances systems of the cell cycle. Without checks and balances, CD4 T lymphocytes develop mutations and increase in numbers, known as lymphocytosis. It may eventually lead to a diagnosis of adult T-cell leukemia/lymphoma.

• TRUCTOR NOTE

Again, the details will be discussed in the Lymphoma session later.
For now just associate the virus with the disease

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Which cell type is primarily affected by HTLV-1?

Bacteria

Bacteria are everywhere! No, really, everywhere! That being said, many bacteria work with you rather than against you. Those that don't tend to go to war with the human body. This war causes inflammation, which can irritate nearby cells and cause them to become cancer. One species in particular that likes to cause problems is *Helicobacter pylori*.

H pylori is a curved, gram-negative, motile, rod-shaped bacterium. *H pylori* infection is not uncommon; in fact, 50% of the world's population is colonized by this organism. However, if the infection is left untreated and becomes chronic, it increases your risk of gastric adenocarcinoma and a particular type of lymphoma called mucosa-associated lymphoid tissue (MALT) lymphoma.

H pylori has multiple virulence factors that allow it to live and colonize in the highly acidic environment of the stomach. The infection induces inflammation, leading to reactive oxygen species, which damage the surrounding cells. In addition, the gastric cells proliferate to create extra layers to protect the underlying mucosa. If the organism is not cleared, the infection becomes chronic.

This constant war between host immunity and *H pylori* transitions the initially developed superficial gastritis to atrophic gastritis (ie, loss of gastric glandular cells and replacement by fibrous tissue). Without successful treatment, the mucosa continues to evolve from the original cell type to a new cell type, known as metaplasia. Then, the new cells exhibit disordered growth, known as dysplasia. If the dysplasia progresses, it may evolve into carcinoma (cancer).

How much of the world's population is colonized by *H pylori*?

Parasites

Parasites—organisms that rely on other organisms to grow and proliferate—can damage their hosts. Sometimes, parasites cause the host to have an immune reaction, flu-like symptoms, or even blindness. Did you know that parasites also can cause cancer? These parasites are located in the Middle East, Africa, and Asia. Inhabitants of and travelers to these countries are at risk. Two types of flatworms and one helminth are known for causing cancer. We will explore the helminth, *Schistosoma haematobium*.

S haematobium is a member of the *Schistosoma* family of parasites. All schistosomes are free-living aquatic parasitic flat worms, also known as helminths. The immature parasite enters the human body via the skin and may present as an itchy skin rash known as “swimmer’s itch.” Then it travels through the bloodstream to the liver, where it matures into the adult phase of its life cycle. It mates with another schistosome, and the eggs exit the body by urine and defecation into the water, where a snail becomes the intermediate host until an immature organism develops and is able to infect another human.

S haematobium has an affinity for the bladder, where it causes urinary schistosomiasis (Figure 5).

Parasites

QUIZ

 Tap image for quiz

Figure 5

Chronic infection results in pain, secondary infections, kidney damage, and bladder cancer. This process is similar to that described in many other organisms. Infection leads to activation of the host's immune system. Insufficient clearance of the organisms by the immune system results in chronic infection. Cyclical infection and immune system response cause inflammation and the production of substances, such as reactive oxygen species, that damage host tissue. Damaged tissue means increased proliferation of new tissue by the host. This development can spiral into metaplasia, then dysplasia, and then carcinoma if not caught in time.

Wrapping Up

INSTRUCTOR NOTE

This table is a good reference. There is no need at this point to know about the specific cancers but please understand the associations of the viruses, bacteria, and parasite to the specific cancers mentioned.

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Wow! Viruses, bacteria, and parasites are small but incredibly powerful organisms that are masters of survival. Refer to Table 1 for a quick review of the key points.

Table 1

| Microorganism | Cell Affected | Mechanism of Cancer Development | Type of Cancer |
|----------------|--|---|---|
| Viruses | | | |
| EBV | B lymphocytes Squamous cells | Opportunistic | Hodgkin lymphoma Burkitt lymphoma Nasopharyngeal carcinoma |
| HHV-8 | Primitive mesenchymal cells B lymphocytes | Altered regulation of VEGF | Kaposi sarcoma Primary effusion lymphoma Multicentric Castleman disease and some multiple myeloma |
| HBV/HCV | Hepatocytes | Chronic inflammation HBV DNA integration | Hepatocellular carcinoma |

| | | | |
|----------------------|--|---|--|
| | | | into hepatocyte |
| HPV | Squamous cells | E6 inactivates p53 E7 inactivates Rb | Cancers of the cervix, vagina, vulva, penis, anus, rectum, and oropharynx |
| HTLV-1 | CD4 T cells | Tax protein | Adult T-cell leukemia/ lymphoma |
| Bacteria | | | |
| <i>H pylori</i> | Gastric epithelial cells Lymphocytes in mucosa-associated lymphoid tissue | Chronic inflammation | Gastric adenocarcinoma Lymphoma |
| Parasites | | | |
| <i>S haematobium</i> | Bladder epithelial cells | Chronic inflammation | Bladder carcinoma |

CASE CONNECTION

[BACK TO INTRODUCTION ↑](#)

Thinking back to RS, what is his diagnosis?

RS has Kaposi sarcoma due to HHV-8. HHV-8 allows for continuous activation of VEGF, resulting in an increase in the formation of blood vessels. These new blood vessels bring nutrients to the skin, which is responsible for the physical appearance of the lesion. RS responds to the treatment for his Kaposi sarcoma and continues taking his multidrug regimen to treat his HIV infection.

Summary

- Viruses, bacteria, and parasites can cause cancer.
- Each of these microorganisms has a specific affinity for a certain cell type.
- The microorganisms have unique mechanisms of action to infect the human host and initiate the development of cancer.
- Viruses cause 12% of all cancers.
- EBV can cause Hodgkin lymphoma, Burkitt lymphoma, and nasopharyngeal carcinoma because of its affinity for B cells.
- HHV-8 causes Kaposi sarcoma and primary effusion lymphoma because of its deregulatory effects on VEGF.
- HBV and HCV target hepatocytes and cause hepatocellular carcinoma.
- HPV uses E6 and E7 to inhibit p53 and Rb, respectively, causing anogenital carcinomas, especially cervical cancer.
- HTLV-1 uses the Tax protein to mutate CD-4 T cells, resulting in adult T-cell leukemia/lymphoma.
- The main cancer-causing bacteria is *H pylori*, which is associated with gastric adenocarcinoma and MALT lymphoma.
- Parasites, like bacteria, cause chronic inflammation and can lead to cancer, such as bladder carcinoma from *S haematobium*.

Review Questions

1. A 13-year-old child presents to you with a large tumor on his jaw. He and his family recently emigrated from Uganda in the hopes of finding him better care. What organism most likely caused this child's tumor?
 - EBV
 - H pylori*