J Bras Patol Med Lab. 2018 Dec; 54(6): 412-418.

10.5935/1676-2444.20180067

Cancer: but what if it were a disease caused by an association between microorganisms?

Câncer: e se for uma doença causada por uma associação entre microrganismos?

Karla Lais Pêgas

Santa Casa de Misericórdia de Porto Alegre, Rio Grande do Sul, Brazil; Hospital Nossa Senhora da Conceição, Rio Grande do Sul, Brazil.

ABSTRACT

Despite the advances in knowledge of the neoplasm behavior, the exact understanding of the biological processes that involve the malignant tumors is not yet fully elucidated. Mechanisms such as subversion of phagocytosis, cytokines and chemokines expression, blocking of immunity and apoptosis regulation are recognized ways of tumor survival. Several of these mechanisms are also used as survival strategies of microorganisms. This article makes an analogy and compares the biological behavior of bacteria, viruses and neoplasms, showing several common points in their mechanisms of growth and survival, questioning cancer as a distinct living organism and introducing the hypothesis of synergy between viruses and bacteria in the development of neoplasms. Up to now, there are no experimental studies that effectively investigate the association between more than one microorganism as an etiologic factor of cancer.

Key words: virus; bacteria; carcinogenesis; immunity; apoptosis; cancer.

INTRODUCTION

Many advances have been made in our understanding on the behavior of cancer, but the exact biological processes involved in the development of malignant tumors have not been fully elucidated yet. The existence of different mechanisms of malignant transformation, such as chemical, physical, and viral carcinogenesis, indicates that cancer is a multifactorial disease. Furthermore, the immune system is involved in cancer development and progression, since it has a close interaction with carcinogenic factors. Current theories on the origin of cancer are focused on the idea that neoplasms of different tissues have diverse etiological mechanisms, based on morphological, biological, and molecular findings. However, by comparing neoplasms of different histological types, we can also find morphological, biological, and molecular similarities between them, which may lend support to the idea of a common etiology that predetermines the type and location of genetic mutations in the cells, as well as subsequent mutations found in malignant cells. Mechanisms of growth and survival of malignant tumors, such as regulation of cell cycle and apoptosis and immune system evasion are well-described strategies of viral growth and replication[1]. In addition, the association between oncoviruses and bacteria is involved in the development of some neoplasms. Despite the viral etiology of different types of cancers, it seems that viruses can contribute, but often are not sufficient for carcinogenesis. In fact, most patients infected with tumorigenic viruses do not develop cancer[2]. The *Helicobacter pylori* model as a carcinogen associates the long-term inflammatory process induced by the infection with gastric adenocarcinoma and lymphomas, especially mucosa-associated lymphoid tissue (MALT). The first associations between neoplasms and bacteria were observed in cases of osteomyelitis, in which the inflammatory process was linked to the development of cancer, but the microorganism was not considered a direct cause of cancer[3]. Many chemical and physical agents are related to the development of cancer, but the question remains as to why some damaged cells do not undergo apoptosis due to their effects. Do these cells have the high degree of autonomy required to undergo malignant transformations? Or do these cells become vulnerable, so that their structure enables a portal of entry of

First submission on 05/19/18; last submission on 08/30/18; accepted for publication on 10/09/18; published on 12/20/18

pathogens capable of altering their genetic material? And are they responsible for the development, growth, and spread of neoplasms? This article aims to show the similar behavior of cancers, viruses, and bacteria, suggesting that infection is the main etiological factor of cancer and discussing the synergy between viruses and bacteria.

ANTI-IMMUNE STRATEGIES OF VIRUSES, BACTERIA, AND NEOPLASMS SHARE THE SAME GOAL: GROWTH AND SPREAD

Eight well studied and documented changes in cellular physiology are considered hallmarks of all types of cancer: self-sufficiency in growth signals (proliferation without external stimuli); insensitivity to growth-inhibitory signals (lack of response to molecules that inhibit cell proliferation by inactivation of tumor suppressor genes); altered cell metabolism (metabolic conversion to anaerobic glycolysis); evasion of apoptosis (resistance to programmed cell death); unlimited replication potential (protection against cell senescence and mitotic catastrophe); induction of angiogenesis; tissue invasion and metastasis (malignancy, involves degradation of the interstitial matrix mediated by proteolytic enzymes, such as metalloproteinases and cathepsins); and evasion of the immune response[4].

Viruses and bacteria, as well as parasites, have developed highly effective mechanisms to subvert the human immune system. Pathogens evolved a plethora of anti-immune strategies to overcome innate and acquired immunity, and these strategies may play a crucial role in their disease-inducing capacity. Although the immunomodulatory mechanisms used by viruses and bacteria may seem very different, there is a surprising number of similarities between them. These pathogens need to circumvent the host's immune response, and they use parallel strategies to evade the immune system[5].

Phagocytosis subversion mechanisms

Several pathogenic bacteria have developed mechanisms to avoid phagocytosis. The capacity of avoiding internalization and death plays a central role in virulence strategy. Internalization of organisms by phagocytosis has three strategic choices to avoid death: they can escape from phagosomes, inhibit phagosome – lysosome fusion, or activate mechanisms that enable their survival inside phagolysosomes. Even though blockade of inflammatory pathways is the predominant survival strategy, some bacteria actually activate inflammatory responses[6-8].

Several viruses have protective mechanisms against the antimicrobial effects of nitric oxide and reactive oxygen species (ROS) generated by activated phagocytes. Some viruses promote the synthesis of inducible nitric oxide synthase (iNOS,) whereas others prevent iNOS production. The iNOS gene is under the control of nuclear factor kappa B (NFκB) and signal transducer and activator of transcription 1 (STAT1), transcription factors that various viruses directly modulate as part of their anti-interferon strategy. Thus, viruses that prevent the induction of interferon type I frequently downregulate iNOS expression, whereas viruses that induce iNOS expression generally stimulate the immunoregulatory or pro-inflammatory properties of nitric oxide to enhance their pathogenesis or dissemination strategy[9-11].

Altered iNOS expression has been detected in several cancers, such as cervical, breast, central nervous system, larynx, and head and neck malignancies. Nitric oxide has been proposed as a modulator in cancer-related events, and several studies have indicated that nitric oxide may have a dual effect on cancer. At concentrations found in several clinical specimens, nitric oxide appears to promote tumor growth and proliferation. Conversely, nitric oxide has also been reported to have antitumor effects. Direct and indirect mechanisms have been proposed to explain the antitumor properties of nitric oxide[12].

Regulation of cytokines and chemokines

There are several reports of bacterial pathogens altering the regulation of inflammatory cytokines, although molecular mechanisms have not been fully elucidated in most cases. However, some pathogens are known to act directly on cytokine pathways to sustain infection. Bacteria are able to block inflammatory pathways, activate alternative pathways, and secrete degraded proteins[5].

Several cytokines, especially interferon, tumor necrosis factors (TNFs), interleukin-1, and members of the chemokine superfamily, are subject to viral modulation. Anti-cytokine proteins produced by viruses include intracellular modulators of gene expression, immune ligand mimics, viral growth factors, membrane-bound cytokine inhibitors, receptor homologs, and pathway regulators that influence the stability, trafficking, or signaling of infected cell receptors[5].

Cancer cells and the immune system overexpress a variety of cytokines in patients with malignancy. Some of these cytokines act as autocrine or paracrine growth factors for the neoplastic tissue, causing fatigue and cachexia symptoms[13]. Studies suggest that tumor necrosis factor alpha (TNF-α) is an essential cytokine

for tumorigenesis in rodent skin and indicate a discrete role of interleukin-1, interleukin-6, and other cytokines in tumor promotion and cell transformation[14].

Suppression of cellular immunity

An important aspect, regarding the early cellular response, is the role of natural killer (NK) cells and how they discriminate between normal host cells and infected or transformed cells. Cell deregulation by viruses has been better studied in chronic infections, such as herpes, but it is likely that even acute viral infections modulate the NK cell function as part of their early anti-immune strategy[5, 15].

Viral strategies against NK cells include expression of major histocompatibility complex (MHC) class I homologue, modulation of MHC expression in infected cells, block of NK cell activation by cytokines, such as interferon type I, antagonism of NK receptor functions, and inhibition of NK effector pathways. In contrast to NK cells, cytotoxic T-cells and helper T-cells express selective antigenic receptors that recognize non-specific epitopes presented in conjunction with MHC molecules. Thus, NK cells provide rapid response to a viral infection, whereas T-cells may take days to weeks to mature, as does their response. Viruses can induce persistent infections that can lead to long-term alterations in the host's immune system. The extent to which a virus modulates the acquired immunity mechanisms varies dramatically according to its particular biology. Autophagy also promotes viral antigen processing via the MHC-II pathway and, due to the potential importance of autophagy in host responses to pathogens, this pathway can also be expected to be manipulated by viruses[5, 15-17].

Most bacterial pathogens try to avoid the acquired immune response, and there are few examples of direct interference with the acquired immunity. For example, *Helicobacter pylori* lipopolysaccharides bind to the C-type lectin DC-SIGN on gastric dendritic cells (DC) to block the development of type 1 T helper (Th1) cells, tilting the immune response from a Th1-based response to a Th1/Th2-mixed response. Another strategy adopted by mucosal pathogens is the secretion of enzymes that degrade immunoglobulins, such as immunoglobulin class A (IgA) proteases[5].

Tumor cells have mechanisms to evade the immune system even in immunocompetent hosts. These mechanisms include: selective growth of antigen-negative variants, in which strongly immunogenic clones are promptly eliminated; absent or reduced MHC expression, in which tumor cells may not express normal levels of MHC-I molecules, thus escaping from cytotoxic T cells; activation of immunoregulatory pathways, in which cancer cells actively inhibit tumor immunity by suppressing regulatory pathways that serve as "checkpoints" in immune reactions; down-regulation of costimulatory factor expression in antigen-presenting cells, such as dendritic cells, which not only avoids cell sensitization but may also induce a long-term lack of response in tumor-specific T cells; secretion of immune response inhibitors, for instance, tumor necrosis factor beta (TNF-β) secreted in large amounts by many types of cancers is a potent immunosuppressant, and some cancers secrete proteins that favor the development of regulatory T cells, which may also contribute to invasion; deregulation of autophagy-inducing pathways, in which tumor cells are frequently able to grow under marginal environmental conditions without triggering autophagy, accordingly, several autophagy-inducing genes are tumor suppressors[4].

Modulation of cell death

When viruses infect somatic cells, their ability to modulate cell death pathways may be crucial for the progression of infection, not only for the virus to complete its replication cycle and spread within the host, but also with regard to how infected cells communicate with the immune system. Viruses may be able to prevent the maturation of antigen-presenting dendritic cells, thus favoring the induction of tolerance to viral antigens. In general, viruses can accelerate or inhibit cell death pathways, depending on the biology of the virus[5].

Several bacterial pathogens also alter apoptotic pathways as part of their virulence strategy. Likewise, viruses are obligate intracellular pathogens that generally inhibit apoptotic death. Because apoptotic death can be less inflammatory than cytotoxic death, several facultative intracellular pathogens choose this strategy to neutralize a variety of host cells. Chlamydiae are obligate intracellular bacteria that reside within a membrane-bound compartment (inclusion) in host cells. These bacteria have developed different strategies to evade the host's immune response and to prevent the initiation of apoptosis in infected cells. These strategies include blocking the release of mitochondrial cytochrome c and inhibiting Bax, Bak, and caspase-3 activation. In addition, chlamydiae degrade pro-apoptotic proteins, such as BH3-only, Bim/Bod, Puma, and Bad, and present other mechanisms of action, well-documented in the literature[5, 18, 19].

Cancer can be considered the result of a series of genetic changes during which a normal cell is transformed into a malignant cell. Evasion of cell death is an essential characteristic

of cells that has mutate. Thus, inhibition or resistance to apoptosis plays an important role in carcinogenesis. A malignant cell can become resistant to apoptosis in many ways, such as by having a disrupted balance of pro-apoptotic (Bid, Bim, Puma, Noxa, Bad, Bmf, Hrk, Bik, BAX, BAK, Bok/Mtd) and anti-apoptotic proteins (Bcl-2, Bcl-xl, Bcl-w, Mcl-1, A1/BF-1, BclB/Bcl2L10), reduced caspase function, or impaired death receptor signaling[20].

Other anti-immune strategies are well described in the literature. Their molecular mechanisms are broad and complex, and it is not the purpose of this study to detail all pathways of immune evasion but rather to make an analogy, showing the similarities between the survival mechanisms of neoplasms and microorganisms. Are these similarities a mere coincidence? We have observed that viruses and bacteria present parallel strategies to neutralize the immune system of a host, as cancer does. Below, we describe some forms of mutual collaboration between viruses and bacteria in pathogenesis. One point is clear: viruses, bacteria, and neoplasms share the same goal – growth and spread.

VIRUS-BACTERIA INTERACTION: AN OVERVIEW

The literature on virus–bacteria interaction is scarce, even more regarding its association with carcinogenesis. The coexistence of bacteria and viruses of eukaryotes in the same host is widely documented; however, their interrelationship and whether they promote or inhibit the presence of one another has only recently gained attention[21].

Bacterial vaginosis (BV) has been associated with human papilloma virus (HPV) infection. A study investigated the relationship between BV and the outcome of HPV infection and concluded that BV-positive women exhibited lower rates of HPV clearance in comparison with women without BV[22]. Another study presented similar results[23]. Only a few HPV infections persist and progress to cervical cancer and BV is a possible risk factor for the acquisition of a chronic HPV infection. These results cannot determine the order of HPV and BV occurrence, but they suggest that bacterial infection prior to HPV infection increases the predisposition to HPV persistence[22].

Another study associated chronic periodontitis and the risk of tongue cancer. Chronic periodontitis is a bacterial-induced chronic inflammation caused primarily by anaerobic bacteria in the dental biofilm. The role of viruses in the initiation and progression of periodontitis has been demonstrated. Viruses and bacteria can act synergistically to cause periodontitis. Some studies suggest that periodontal pockets serve as reservoirs for HPV, cytomegalovirus, and Epstein-Barr virus – pathogens suspected of having an association with oral cancer. Gingival biopsies of patients with periodontal disease showed the presence of high-risk HPV[24]. Research evidenced that aggressive periodontitis is the result of interactions between three types of herpes viruses (Epstein-Barr virus type 1, cytomegalovirus, and herpes simplex virus) and the periodontal bacteria *Porphyromonas gingivalis* and *Dialister pneumosintes*. Collaboration between viruses and bacteria serves a dual purpose: to weaken the immune system and to develop the lesion. Herpes simplex virus and cytomegalovirus infect monocytes, macrophages, and T lymphocytes, whereas Epstein-Barr virus type 1 targets B-lymphocytes. Virus-infected immune cells cause inflammation and cytopathic effects in the host tissue, resulting in a decreased defense ability against periodontal bacteria[25].

Recently, *Fusobacterium nucleatum* infection was reported to be prevalent in colorectal carcinomas. *Fusobacterium nucleatum* is an invasive, adherent, and pro-inflammatory anaerobic bacterium. It is common in dental plaque and has been associated with periodontitis. An unexpected over-representation of *Fusobacterium nucleatum* was observed in colorectal tumors, as it is not an abundant microorganism of the normal intestinal microbiota. It has not yet been determined whether *Fusobacterium nucleatum* is involved in tumorigenesis[26].

In a recent review, Müller-Coan *et al*. (2018)[27] emphasize the role of some viruses in malignant transformation by focusing on three main mechanisms of action: the first category relies on the induction of genetic instability, favoring more aggressive clones and prone to metastasis. The second category applies to oncoviruses that render the tumor microenvironment more suitable for cell invasion and dissemination, and the third category includes mechanisms involving change in cell phenotype.

Bakhoum *et al*. (2018)[28], in an experimental study, shows a link between chromosomal instability (CIN), chronic activation of cytosolic deoxyribonucleic acid (DNA) sensing pathways and metastasis. They separate samples according to their CIN status. Metastasis related and epithelial-to-mesenchymal transition (EMT) genes were relatively enriched in CIN-Hight cells, and they suggest that CIN drives a subset of human metastasis characterized by EMT and inflammation.

On the other hand, microbes upregulated gene transcription factor involved in the regulation of the EMT, and there is a link between microbes and EMT induction at the crossroad of inflammation and cancer[29].

In an experimental study, Leone *et al*. (2016)[30] monitored the ability of *K. pneumonia* to activate the expression of genes related to EMT-like processes.

There is a description of *Pseudomonas aeruginosa* enhancing EMT in the airways and *Helicobacter pylori* promoting EMT in non-transformed epithelial cell models[31].

Some reports associate co-infection with Epstein-Barr virus and *Helicobacter Pylori* in peptic ulcer disease and gastric carcinoma[32-35].

Cardenas-Mondragon *et al*. (2015)[32] suggest that the Epstein-Barr virus co-participates with *Helicobacter pylori* to induce inflammation and the risk of progression of intestinal-type gastric carcinoma.

The presence of viruses in infections previously attributed solely to bacteria has been reported. As well as periodontal disease, reports have confirmed virus-bacteria interaction in the development of acute otitis media. Several studies have shown that the inflammation of the upper respiratory tract has an impact on bacterial colonization of the nasopharynx and bacterial adherence to epithelial cells. Mixed viral-bacterial infections account for 15% of cases of acute otitis media[36].

Bacteria and viruses interact by one benefiting the other. Viruses are generally benefitted by direct interaction with bacteria; they bind to a bacterial cell or use bacterial products. These interactions promote viral infections with no known benefit to bacterial species. On the other hand, bacteria are usually benefitted indirectly; the virus inflicts damage to host cells critical for viral infection, which is also beneficial to other pathogens. Four other mechanisms of indirect interaction can occur, often concomitantly: I. viruses induce an increase in the number of receptors on the bacterial cell surface; II. viruses damage underlying epithelial cells; III. viruses displace commensal bacteria; and IV. viruses suppress the host immune system[26]. There are additional benefits to virus-bacteria interactions other than the direct progression of the disease. Studies have shown that the association with fecal microbiota increases the stability and environmental ability of poliovirus and that exposure to bacteria or their polysaccharides reduces the effectiveness of thermal treatment against poliovirus, potentially helping its survival in the microenvironment[37]. Bacteria often benefit from viral infections. When microbial populations are affected, niches previously inaccessible to pathogens become available, and surfaces where native microbiota previously outcompete their disease-causing counterparts are compromised. Overall, viruses aid bacterial pathogenesis through a complex combination of cell receptor upregulation, disruption of epithelial layers, displacement of commensal bacteria, and immune system suppression[25].

Another interesting type of virus-bacteria interaction results in the subversion of the immune system, which occurs when viruses target cells such as lymphocytes, macrophages, and monocytes. Infection and replication within these cells strongly affects the immune response of the host[38]. Viruses modulate Toll-like receptor pathways, resulting in a decrease in neutrophil attraction to bacteria, increasing bacterial adherence to cells. In addition, viral infections such as influenza can disrupt the production of cytokines by inducing the production of interferon type I, a down regulator of cytokine production[39, 40].

The subversion of the immune system is dynamic and should be considered when studying virus-bacteria interaction concerning pathogenesis. An increase in pathogenicity occurs as a consequence of virus-bacteria interactions in areas normally inhabited by normally benign members of the native microflora. Viruses utilize bacterial components to enter target cells, whereas bacteria take advantage of the destructive nature of viral replication to obtain advantages in previously inaccessible regions. Within the body, these organisms can act synergistically to improve their action, to the detriment of the host[25].

WHAT IS CANCER?

But what if we imagined cancer as the result of a large, well-planned ‘‘kidnapping’’ of the energetic supply by organisms that otherwise would have no way of obtaining it? Conversely, there is a multicellular organism in a state of homeostasis with energy, supplement, and nutrient exchanges, and there are obligate intracellular parasite organisms requiring a host for survival. For many different reasons and mechanisms not fully understood, the common proverb ‘‘opportunity makes a thief’’ could be applied. The immune defense system contributes to the preservation of homeostasis; even so, various agents that could render them vulnerable and facilitators are constantly damaging some cells. Nevertheless, how would this ‘‘kidnapping’’ work? Would viruses and bacteria use complementary mechanisms to penetrate vulnerable cells, couple their genetic code, become invisible to the immune system and, through successive induced cell mutations, multiply and propagate? Many complementary mechanisms could be used to shift cells in homeostasis toward uncontrolled growth. In a struggle for survival, could viruses and bacteria synergistically produce toxins, induce extracellular matrix degradation, inhibit phagocytosis, autophagy, apoptosis, and inflammatory pathways, activate signaling pathways, among many others mechanisms of survival?

What is cancer? Is it a group of mutated cells that were no longer part of the team, competing with others for the host's nutrients, or is cancer a distinct living organism (or organisms)? Why do cells that survive target therapies develop alternative growth mechanisms[41], if it were not because they are orchestrated by manipulative structures?

This article aims to suggest a new way of thinking about cancer. The hypothesis of synergy between viruses and bacteria as an etiological factor in cancers may open the way to new understanding neoplasms and for the development of target therapies as well as preventive immunization.

There are no reports in the literature about this association and, therefore, there is no concrete evidence to substantiate this hypothesis.

The author suggests that the hypothesis of a virus-bacteria synergy in the development of neoplasms should be tested in experimental studies.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

The author has no conflict of interest to declare.

RESUMO

Apesar dos avanços no conhecimento do comportamento das neoplasias, o entendimento exato dos processos biológicos que envolvem os tumores malignos ainda não está totalmente elucidado. Mecanismos como subversão da fagocitose, expressão de citoquinas e quimiocinas, bloqueio da imunidade e regulação da apoptose são vias conhecidas de sobrevivência dos cânceres. Vários desses mecanismos também são utilizados como estratégias de sobrevivência de microrganismos. Este artigo faz uma analogia e compara o comportamento biológico das bactérias, dos vírus e das neoplasias, mostrando vários pontos em comum nos seus mecanismos de crescimento e sobrevivência, questionando o câncer como um organismo vivo distinto e introduzindo a hipótese de sinergia entre vírus e bactérias no desenvolvimento das neoplasias. Não há, até o momento, estudos experimentais que investiguem efetivamente a associação entre mais de um microrganismo como fator etiológico do câncer.

Unitermos: *vírus; bactérias; carcinogênese; imunidade; apoptose; neoplasias.*

REFERENCES

1. McLaughlin-Drubin ME, Munger K. Virus associated with human cancer. Biochim Biophys Acta. 2008; 1782(3): 127-50.

2. Cohen SM. Microbes and malignancy: infection as a cause of human cancers. Parsonnet J, editor. Oxford, UK: Oxford University Press; 1999. p. 89-106.

3. Parsonnet J. Bacterial infection as a cause of cancer. Environ Health Perspect. 1995; 103(suppl 8): 263-8.

4. Kumar V, Abbas A, Aster JC. Robbins and cotran pathologic basis of disease. 9th edition. New York, NY: Elsevier. p. 269-347.

5. Finlay BB, McFadden G. Anti-immunology: evasion of the host immune system by bacterial and viral pathogens. Cell. 2006; 124(4): 767-82.

6. Celli J, Finlay BB. Bacterial avoidance of phagocytosis. Trends Microbiol. 2002; 10: 232-7.

7. Rosenberger CM, Finlay BB. Phagocyte sabotage: disruption of macrophage signaling by bacterial pathogens. Nat Rev Mol Cell Biol. 2003; 4(5): 385-96.

8. Portnoy DA. Manipulation of innate immunity by bacterial pathogens. Curr Opin Immunol. 2005; 17(1): 25-8.

9. Bowie AG, Zhan J, Marshall WL. Viral appropriation of apoptotic and NF-kappaB signaling pathways. J Cell Biochem. 2004; 91: 1099-108.

10. Weber F, Kochs G, Haller O. Inverse interference: how virus fight the interferon system. Viral Immunol. 2004; 17: 498-515.

11. Foster-Cuevas M, Wright GJ, Puklavec MJ, Brown MH, Barclay AN. Human herpes virus 8 k14 protein mimics cd200 in down-regulating macrophage activation through cd200 receptor. J Virol. 2004; 78(14): 7667-76.

12. Choudhari SK, Chaudhary M, Bagde S, Gadbail AR, Joshi V. Nitric oxide and cancer: a review. World J Surg Oncol. 2013; 11: 118.

13. Han J, Meng Q, Shen L, Wu G. Interleukin-6 induces fat loss in cancer cachexia by promoting white adipose tissue lipolysis and browning. Lipids Health Dis. 2018; 17(1): 14.

14. Suganuma M, Okabe S, Kurusu M, et al. Discrete roles of cytokines, TNF-alpha, IL-1, IL-6 in tumor promotion and cell transformation. Int J Oncol. 2002; 20(1): 131-6.

15. Dorner BG, Smith HR, French AR, et al. Coordinate expression of cytokines and chemokines by NK cells during murine cytomegalovirus infection. J Immunol. 2004; 172(5): 3119-31.

16. Klenerman P, Hill A. T cells and viral persistence: lessons from diverse infections. Nat Immunol. 2005; 6(9): 873-9.

17. Deretic V. Autophagy in innate and adaptive immunity. Trends Immunol. 2005; 26(10): 523-8.

18. Guiney DG. The role of host cell death in salmonella infection. Curr Top Microbiol Immunol. 2005; 289: 131-50.

19. Fan T, Lu H, Hu H, et al. Inhibition of apoptosis in chlamydia-infected cells: blockade of mitochondrial cytochrome c release and caspase activation. J Exp Med. 1998; 187(4): 487-96.

20. Wong RS. Apoptosis in cancer: from pathogenesis to treatment. J Exp Clin Cancer Res. 2011; 30(1): 87.

21. Moore MD, Jaykus LA. Virus-bacteria interactions: implications and potential for the applied and agricultural sciences. Viruses. 2018; 10(2): E61.

22. Guo YL, You K, Qiao J, Zhao YM, Geng L. Bacterial vaginosis is conducive to the persistence of HPV infection. Int J STD AIDS. 2012; 23(8): 581-4.

23. King CC, Jamieson DJ, Wiener J, et al. Bacterial vaginosis and the natural history of human papillomavirus. Infect Dis Obstet Gynecol. 2011; 2011: 319-460.

24. Tezal M, Sullivan MA, Reid ME, et al. Chronic periodontitis and the risk of tongue cancer. Arch Otolaryngol Head Neck Surg. 2007; 133(5): 450-4.

25. Almand EA, Moore MD, Jaykus LA. Virus-bacteria interactions: an emerging topic in human infection. Viruses. 2017; 9(3).

26. Castellarin M, Warren RL, Freeman JD, et al. Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Genome Res. 2012; 22(2): 299-306.

27. Müller-Coan BD, Caetano BFR, Pagano JS, et al. Cancer progression goes viral: the role of oncoviruses in aggressiveness of malignancies. Trends Cancer. 2018; 4(7): 485-98.

28. Bakhoum SF, Ngo B, Laughney AM, et al. Chromosomal instability drives metastasis through a cytosolic DNA response. Nature. 2018; 553(7689): 467-72.

29. Hofman P, Vouret-Craviari V. Microbes-induced EMT at the crossroad of inflammation and cancer. Gut Microbes. 2012; 3(3): 176-85.

30. Leone L, Mazzetta F, Martinelli D. Klebsiella pneumoniae is able to trigger epithelial-mesenchymal transition process in cultured airway epithelial cells. PLoS One. 2016; 11(1): e0146365.

31. Borthwick LA, Sunny SS, Oliphant V, et al. Pseudomonas aeruginosa accentuates epithelial-to-mesenchymal transition in the airway. Eur Respir J. 2011; 37(5): 1237-47.

32. Cardenas-Mondragon MG, Torres J, Flores-Luna L, et al. Case-control study of Epstein-Barr virus and Helicobacter pylori serology in Latin American patients with gastric disease. Br J Cancer. 2015; 112(12): 1866-73.

33. Cardenas-Mondragon MG, Carreon-Talavera R, Camorlinga-Ponce M, et al. Epstein-Barr virus and Helicobacter pylori co-infection are positively associated with severe gastritis in pediatric patients. PLoS One. 2013; 8(4): e62850.

34. de Souza CR, de Oliveira KS, Ferraz JJ, et al. Occurrence of Helicobacter pylori and Epstein-Barr virus infection in endoscopic and gastric cancer patients from Northern Brazil. BMC Gastroenterology. 2014; 14: 179.

35. Saxena A, Nath Prasad K, Chand Ghoshal U, et al. Association of Helicobacter pylori and Epstein-Barr virus with gastric cancer and peptic ulcer disease. Scand J Gastroenterol. 2008; 43(6): 669-74.

36. Heikkinen T, Chonmaitree T. Viral-bacterial synergy in otitis media: implications for management. Curr Infect Dis Rep. 2000; 2(2): 154-9.

37. Robinson CM, Jesudhasan PR, Pfeiffer JK. Bacterial lipopolysaccharide binding enhances virion stability and promotes environmental fitness of an enteric virus. Cell Host Microbe. 2014; 15(1): 36-46.

38. Karst SM. The influence of commensal bacteria on infection with enteric viruses. Nat Rev Microbiol. 2016; 14(4): 197-204.

39. Hendaus MA, Jomha FA, Alhammadi AH. Virus-induced secondary bacterial infection: a concise review. Ther Clin Risk Manag. 2015; 11: 1265-71.

40. Mehta D, Petes C, Gee K, Basta S. The role of virus infection in deregulating the cytokine response to secondary bacterial infection. J interferon Cytokine Res. 2015; 35(12): 925-34.

41. Jones VS, Huang RY, Chen LP, Chen ZS, Fu L, Huang RP. Cytokines in cancer drug resistance: clues to new therapeutic strategies. Biochim Biophys Acta. 2016; 1865(2): 255-65.

CORRESPONDING AUTHOR

Karla Lais Pêgas

Laboratório de Patologia e Micologia; Hospital Santa Rita, 2º andar; Avenida Sarmento Leite, 187; Centro Histórico; CEP: 90050-170; Porto Alegre-RS, Brasil; e-mail: lfp.voy@terra.com.br.