ISSN 2219-2824 (online)

World Journal of *Immunology*

World J Immunol 2017 July 27; 7(2): 11-31

Published by Baishideng Publishing Group Inc

World Journal of Immunology

Contents

Four-monthly Volume 7 Number 2 July 27, 2017

REVIEW

MINIREVIEWS

World Journal of Immunology
Volume 7 Number 2 July 27, 2017

Contents

NAME OF JOURNAL
World Journal of Immunology

ISSN
ISSN 2219-2824 (online)

LAUNCH DATE
December 27, 2011

FREQUENCY
Four-monthly

EDITORIAL OFFICE
Fang-Fang Ji, Director
World Journal of Immunology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
July 27, 2017

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Immunology

Submit a Manuscript: http://www.f6publishing.com

World J Immunol 2017 July 27; 7(2): 11-23

DOI: 10.5411/wji.v7.i2.11

ISSN 2219-2824 (online)

REVIEW

Holistic paradigm in carcinogenesis: Genetics, epigenetics, immunity, inflammation and oral infections

Sok-Ja Janket, Marium Qureshi, Antonio Bascones-Martinez, Jerian González-Febles, Jukka H Meurman

Sok-Ja Janket, Department of Periodontology, Boston University H. M. Goldman School of Dental Medicine, Boston, MA 02118, United States

Sok-Ja Janket, Marium Qureshi, Department of General Dentistry, Boston University H. M. Goldman School of Dental Medicine, Boston, MA 02118, United States

Antonio Bascones-Martinez, Jerian González-Febles, Department of Oral Medicine and Surgery, Complutense University, 28040 Madrid, Spain

Jukka H Meurman, Department of Oral and Maxillofacial Diseases, University of Helsinki and Helsinki University Hospital, 02160 Helsinki, Finland

Author contributions: All authors contributed to this paper.

Supported by Helsinki University Hospital funds, No. TYH2015323 (to Meurman JH).

Conflict-of-interest statement: The authors declare no conflict of interest associated with this paper.

Manuscript source: Invited manuscript

Correspondence to: Sok-Ja Janket, DMD, MPH, Department of Periodontology, Boston University H. M. Goldman School of Dental Medicine, 100 East Newton Street, Room B08A, Boston, MA 02118, United States. skjanket@bu.edu
Telephone: +1-617-4141066
Fax: +1-617-4141061

Received: January 8, 2017
Peer-review started: January 12, 2017
First decision: February 16, 2017
Revised: February 25, 2017
Accepted: April 4, 2017
Article in press: April 7, 2017
Published online: July 27, 2017

Abstract

Recent debate among the experts of cancer research regarding the main causes of carcinogenesis encouraged us to review the etiology of cancer pathogenesis. The somatic mutation theory attributes carcinogenesis to random errors in DNA multiplication while the tissue organization field theory ascribes causation to environmental factors. We recognize complexity in cancer pathogenesis and accept the premise of both DNA multiplication errors and environmental factors in cancer development. Furthermore, it should also be noted that the combination of these factors and the relative importance of the each differ in various types of cancers. For example, in some cancers, genetics plays a prominent role while in others environment such as obesity plays a much stronger role. Additionally, the cancer mitigating factors should also be considered. The balance of cancer-enhancing and cancer-suppressing forces determines the cancer incidence. Ultimately, identifying the lifestyle factors that revise somatic mutations or epigenetic alterations will lead to a clear understanding of pathogenic mechanisms of cancer and to the optimal preventive strategies. This narrative review evaluates the published evidence on carcinogenesis pertaining to the whole organism (thus, holistic) incorporating genetics, epigenetics, immunology, inflammation and infections with emphasis on oral infections.

Key words: Genetics; Carcinogenesis; Inflammation; Epigenetics; Immunity; Infections

Core tip: A recent debate among renowned scholars prompted us to review cancer pathogenesis in a holistic approach. One group attributed cancer to "random errors in DNA multiplication" (Tomasetti C, *Science*, 2015) while other experts credited environmental factors for cancer causation (Wu S, *Nature*, 2016). However, we put forward the concept that cancer is multifactorial and both intrinsic (DNA multiplication errors) and extrinsic (environmental) factors contribute to carcinogenesis. In this review, we examined these risk factors in some detail covering genetics, epigenetics, immunity, inflammation and infections. We acknowledge the contribution of each risk factor is different in various types of cancer. In some cancers, genetics plays a powerful role while in others, metabolism contributes a stronger impact. Therefore, a holistic understanding of carcinogenesis is truly necessary considering multi-system involvement in cancer development.

Janket SJ, Qureshi M, Bascones-Martinez A, González-Febles J, Meurman JH. Holistic paradigm in carcinogenesis: Genetics, epigenetics, immunity, inflammation and oral infections. *World J Immunol* 2017; 7(2): 11-23 Available from: URL: http://www.wjgnet.com/2219-2824/full/v7/i2/11.htm DOI: http://dx.doi.org/10.5411/wji.v7.i2.11

INTRODUCTION

Approximately 1.5 million new cases of cancer are diagnosed each year[1] and nearly 600000 persons will die from the disease[1]. Recent debate among experts[2,3] on carcinogenesis can be categorized into two major theories: Bad luck in DNA multiplication[2] or environmental factors[3]. Somatic mutation theory (SMT) is in support of the thesis that all cancers are caused by somatic mutations[4], namely as consequences of errors in DNA replication. However, a new tissue organization field theory (TOFT) paradigm considers that carcinogenesis takes place at the tissue level, and carcinogenesis is a reversible process[5].

The ever increasing rates of cancer in the last century can be explained by the concurrent burgeoning endocrine-metabolic, inflammatory, neurodevelopmental or neurodegenerative chronic diseases and their epigenetic influence on tissue programming. The somatic mutations can lead to changes at the cellular, genetic, and epigenetic levels that transform normal cells to a malignant mass by permitting and promoting uncontrolled cell division[6]. The somatic mutations include: (1) substitutions of one base for another; (2) insertions or deletions of small or large segments of DNA; (3) re-arrangements, in which DNA has been broken and then rejoined to a different DNA section; (4) gene amplification which increases gene numbers from normal diploids to ploidy of several hundred; or (5) total deletion of genes[7]. Cancer cells may also acquire totally foreign DNAs from viruses. The DNA contributing viruses are human papilloma virus (HPV), human herpes virus 8, Epstein Barr virus, and hepatitis B virus[7]. On the contrary, TOFT considers cancer "results of a disruption of cell communication needed to maintain normal tissue structure and function"[8].

Additionally, epigenetics is a process where external or environmental factors silence some gene expression or enhance others and thus can increase or decrease cancer occurrence. However, epigenetic changes are correlated with gene mutation and the demarcations between genetics and epigenetics become unclear[9,10]. Our opinion is that both genome based SMT and epigenome based TOFT are interlaced in carcinogenesis and that genetics and epigenetics converge in the end. This interpretation has been shared by several leading researchers[10,11]. One point of note is that in some cancers the genome may have more powerful impacts while in others the epigenome may influence carcinogenesis more strongly.

Lifestyle and biologic factors can also modify somatic mutations. These factors include ageing, smoking, alcohol intake, exposures to ultraviolet light or chemicals such as pesticides, obesity and infections[12]. Thus, the progressive accumulation of minor mutations in the normal aging process also increases the risk of cancer. For this reason, ageing is the biggest cancer risk that affects everyone. Because many cancers occur from or in the vicinity of inflammation sites, inflammation was hypothesized to coordinate carcinogenesis[13]. However, this concept was largely invalidated by a disappointing failure of the trials to suppress inflammation for the purpose of reducing cancer incidence[14].

Recent theory suggests that cancer initiation is driven by a disruption in the quorum sensing mechanism, either by genetic mutations, or by the environment[8]. Quorum sensing (QS) can be interpreted as a communication and response mechanism in a community of cells that maintains the integrity of the community. When QS disruption causes dysfunction in sensing, it weakens the tissue defense and the community is vulnerable to cancer development[8]. The majority of QS disruption does not cause cancer because the immune system quickly removes aberrant and undesirable molecules before they progress to malignancy. These findings confirm that immune dysfunction can be an integral part of oncogenesis[15]. Thus, holistic understanding of carcinogenesis is the key to the prevention of cancer. The underlying cancer biology should include: (1) genome instability; (2) evading immune destruction; (3) infection/inflammation; and (4) energy metabolism. Clearly, cancer is a multifactorial disease as we illustrated in Figure 1 but the relative importance among these factors in cancer pathogenesis is yet to be elucidated. If the number of publications may reflect the relative importance, it will be of interest to tabulate the publication metric which is presented in Table 1. We will discuss these multisystem involvements in carcinogenesis individually in some detail.

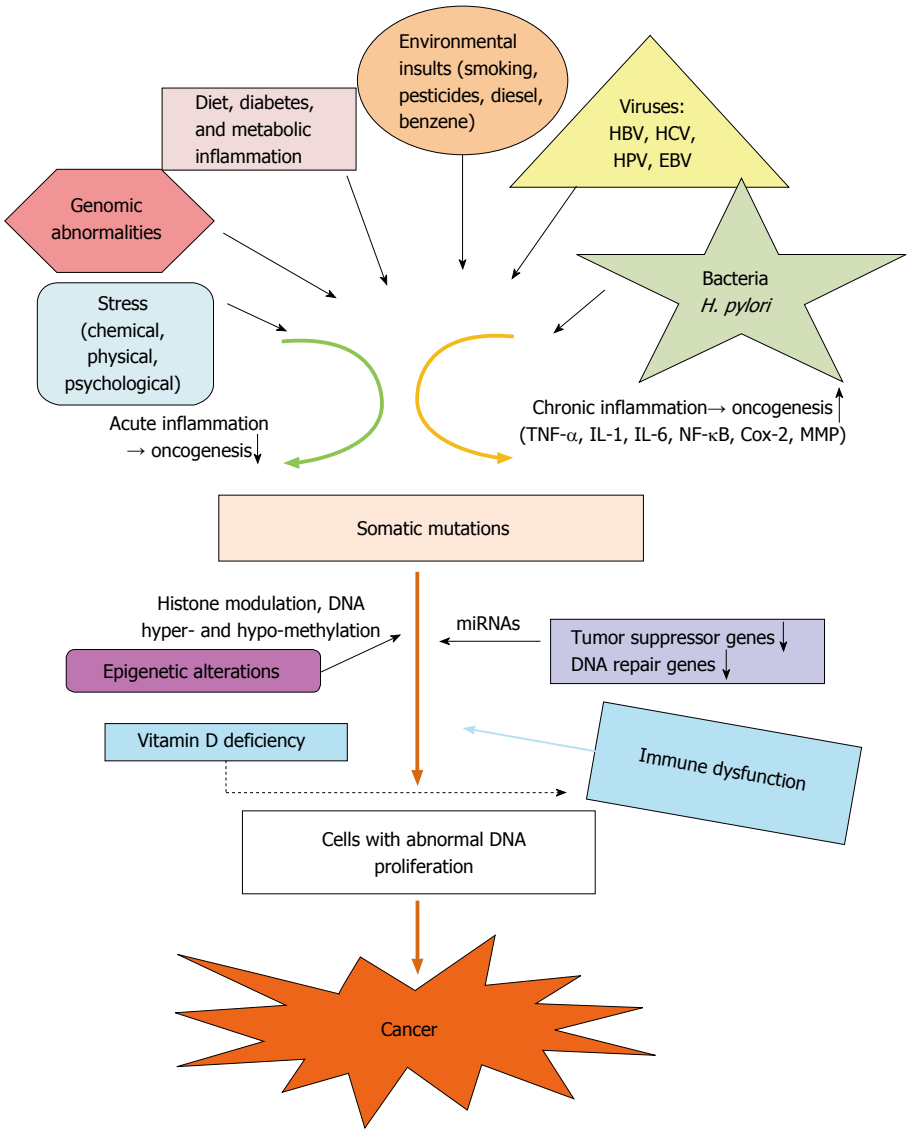

Figure 1 Postulated mechanism of carcinogenesis. HBV: Hepatitis B virus; HCV: Hepatitis C virus; HPV: Human papilloma virus; EBV: Epstein Barr virus; TNF: Tumor necrosis factor; IL: Interleukin; NF-κB: Nuclear factor-κB; MMP: Matrix metalloproteinase; *H. pylori*: *Helicobacter pylori*; miRNAs: MicroRNAs; Cox: Cyclo-oxygenase.

IMMUNOLOGY OF ONCOGENESIS

According to the currently accepted paradigm, the immune system has the ability to regulate cancer initiation and progression while cancer cells have the ability to evade immune actions by expressing molecules that will incapacitate immune intervention. Thus, understanding and manipulating this dynamic relationship became the focus of current cancer therapies.

The innate immune system plays an important role in cancer development. When immune surveillance is normal, the innate immune system quickly triages the stimuli by correctly identifying whether they are harmless, part of the self, or harmful. Typically, appropriate actions will follow, namely, tolerance if harmless and part of self, or destruction if harmful[16,17]. Unfortunately, cancer cells can manipulate immune cells such as macrophages and T-cells to their advantage and deceive them to tolerate aberrant cancer cells by creating immune privileged micro-environments. This is clearly demonstrated by normally host defensive and cancer suppressing macrophages can subvert normally M1 type actions and shift to M2 type activities[18]. This alteration in macrophages' role results in cancer promoting tumor-associated macrophages (TAMs) which express much lower levels of cytotoxic cytokines than its M1 counterpart[19]. M1 pathways are pro-inflammatory, bactericidal, and tumoricidal and thus tumor suppressive. However, M2 pathway promotes anti-inflammatory activities expressing cytokines such as IL-10, transforming growth factor-β and IL-4. Moreover, M2 macrophages are poor antigen presenters and diminish T-cell functions. Additionally, TAMs support wound healing and tissue repair that are favorable to tumorigenesis. These facts strongly indicate that macrophages can be either pro- or anti-inflammatory depending on the environment they

Table 1 Cancer pathogenesis literature metrics stratified by risk factor categories

Risk factor category	No. of articles published
Genetics	379694
Infections	85420
Immunity	52889
Epigenetics	43505
Inflammation	37930
Oral infections and periodontitis	5612

Not all publications report causal relationship.

are situated[20]. TAMs in cancer microenvironment are involved in DNA damage, oncogenic transformation in the pre-tumor stage and promote cell proliferation and survival of tumor cells in established malignancy[21]. TAMs within the cancer microenvironment play crucial roles in oncogenesis, metastasis and manipulation of the adaptive immune system by manipulating effective T-cells[22].

The two important molecules that suppress T-cell function are cytotoxic T-lymphocyte antigen 4 (CTLA-4) and the programmed cell death protein-1 (PD-1)[23]. The cancer cells express PD-L1, a PD-1 ligand, and when PD-L1 binds PD-1, this complex becomes the inhibitors of T and B cell responses. PD-L1 and PD-L2 are upregulated in head and neck squamous cell carcinoma (HNSCC) cells cultured with an oral pathogen, *Porphyromonas gingivalis (P. gingivalis*) *in vitro.* However, co-culturing with *Streptococcus salivarius* K12 did not upregulate PD-L1 or PD-L2[24].

Through these mechanisms the immune system can be forced to tolerate even non-self-antigens, and cancers occur when coexisting epigenetic mutations allow neo-antigens to proliferate. These facts underscore the intimate relationship of the immune system and cancer pathogenesis. Better understanding of the immune system and tumor cells relationship has introduced several novel cancer therapies utilizing immune checkpoint blockades and encouraging the immune system to target the specific cancer cells while leaving other cells and tissues intact[25]. These are the cutting edge bases for the personalized immunotherapy in cancer treatment.

Immunoediting, the basis for individualized cancer therapy

Immunoediting can be defined as "the interactions between the innate and adaptive immune system and cancer cells to restructure the course of cancer progression". Immunoediting can be host-protective (and thus suppressing cancer) or tumor-promoting by establishing a favorable tumor microenvironment that facilitates tumor growth.

The "3 Es" in immunoediting

Elimination: Elimination occurs when the immune system is competent and strong enough to produce powerful immune reactions. Under the attack of a strong immune system, tumor cells express stress-induced molecules that are recognized by CD8+ effector cells and natural killer (NK) cells. Activated effector cells can express IFN-γ that inhibits tumor cell proliferation, and angiogenesis and CD8+ T cells can induce tumor cell apoptosis. Thus, tumor cells are completely eliminated[26].

Equilibrium: In the second scenario, immune destruction of cancer cells is not complete but tumor cells do not proliferate and stay dormant. Cancer eliminating cytokines such as IL-12 and IFN-γ are balanced by the action of cancer-tolerant IL-10 and IL-23. Other cytokines such as IL-4, IL-17A, IFN-α/β and NK cells stay out of this battle.

Escape: In the third scenario, tumor cells escape the immune assaults and proliferate. Tumor cells avoid immune recognition *via* weaker tumor antigens, or loss of MHC class Ⅰ as well as the lack of co-stimulatory molecules. In this condition, the cancer cells increase resistance to apoptosis through several mechanisms: (1) by expressing STAT-3 or anti-apoptotic molecule Bcl2; (2) by creating immunsuppressive microenvironments by expressing vascular endothelial growth factor, transforming growth factor beta; or (3) by producing immunoregulatory molecules such as PD-1/PD-L1 complexes that suppress T-cell actions[26].

Individualized immunotherapies

Currently popular cancer treatment strategies include "targeted immunotherapies"[25]. Fundamental principles of this strategy are awakening the checkpoints designed to suppress an over-zealous immune system to prevent autoimmunity. These check points involve molecules such as CTLA-4 and PD-1. By blocking these T-cell inhibitor molecules, T-cells can be energized and encouraged to attack tumor cells[27]. The FDA approved several targeted cancer therapies, namely ipilimumab, a monoclonal antibody against CTLA-4 in 2011, PD-1 antibodies pembrolizumab and nivolumab in 2014, and PD-L1 inhibitor atezolizumab in 2016.

Basic understanding on immunological and inflammatory findings in relation to carcinogenesis is presented in Table 2.

GENETICS IN ONCOGENESIS

Epigenetics and cancer

Epigenetics is defined as genetic control by factors other than an individual's DNA sequence *via* silencing certain genes while promoting others. These processes involve regulating transcription factors, access to chromatin, chromatin-chromatin interactions, expressing microRNAs (miRNA) or long non-coding RNAs (lncRNA) that control the expression of mRNA[28]. One may be tempted to say that epigenetics controls gene expression. However, epigenetic manifestations such

Table 2 Summary of inflammation and cancer relationship

Basic observations	Interpretation
Chronic inflammation increases cancer risk	Causality is not proven[47] Inflammation from psoriasis actually reduces cancer risk
AIs decrease cancer	AIs are proven to decrease cancer risk as shown in Coley's toxin[93] AIs may mobilize strong immune responses and create cancer resisting environment[94,95]
Metabolic inflammation may be an important risk factor	Causality is quite possible, *via* IGF, VEGF
Various type of immune, inflammatory cells are present in cancer loci	They can be innocent bystanders
Immune cells affect malignant cells through cytokines, chemokines, growth factors, prostaglandins, and reactive oxygen and nitrogen species	This fact proves that there is an interaction between immune cells and cancer cells but causal relationship is yet to be established
Inflammation is present from tumor initiation to metastasis	It does not mean inflammation causes cancer. Inflammation may be a part of disease processes in cancer
NF-κB signaling pathway can be two-way street: NF-κB from immune system can suppress cancer progress; also NF-κB from cancer cells to resist immune action Certain immune/inflammatory actions are dispensable in some stages and indispensable in others	NF-κB is universal biologic transcription factor and difficult to prove its involvement as a causal factor in carcinogenesis

AIs: Acute infections; IGF: Insulin-like growth factor; VEGF: Vascular endothelial growth factor.

as histone modification are often strongly correlated with patterns of inherited gene expression[9] and many gene mutations control the epigenome[10], thus, the demarcation between genetics and epigenetics is not clear. Consequently, some researchers regard that genetics and epigenetics are two sides of the same construct and should be combined[10]. During the process of tumor initiation and progression, the cancer epigenome is remodeled *via* global hypomethylation, increased promoter methylation at CpG islands, global down-regulation of miRNAs, lncRNAs or interactions between them and alterations in the nucleosome. The imbalance between transcriptionally permissive and repressive chromatin modifications may alter gene expression and lead to cancer[29].

The role of oral infections in oncogenesis remains ill-defined, however. It has been hypothesized that chronic inflammation such as in periodontitis has the potential to provoke epigenetic modifications[30] leading to DNA and histone methylations that contribute to oncogenesis. However, any bone modulation will involve these histone modifications[28], and periodontitis, which involves bone loss, may also cause histone modulation.

Histone modulation, DNA methylation and other gene alterations

DNA methylations occurring in the CpG islands where the clusters of CpG sequences appear in the promoter regions, prevent transcriptional initiation and silence the genes[31]. Differential methylation patterns associated with apoptosis, lipopolysaccharides (LPS) signaling, cell adhesion and oncogenesis have been observed in untreated periodontitis tissues[30]. DNA methylation is necessary for normal cell development and is essential in tissue specific gene transcription[32]. Histone acetylation and down regulation of DNA methyltransferase 1 (DNMT1) was reported in oral dysbiosis[33]. This study has proven that epigenetic changes may indeed be associated with oral dysbiosis. DNMT1 is overexpressed in many cancers[34]. Thus, reduced DNMT1 in oral dysbiosis is not in agreement with the trend fostering oncogenesis. Parenthetically, reduced DNMT1 is in the same direction of cancer inhibition drugs such as 5-azacitidine or decitabine. Additionally, other lifestyle factors such as protein-restricted diets and weight loss also reduced DNMT1 expression[35]. These observations suggest that DNA methylation may be confounded by metabolic inflammation[17].

In general, histone acetylation is associated with enhanced transcription of genes[31], nucleosome assembly, chromatin folding, DNA damage repair, and replication[36]. However, the location and the gene involved will determine supporting or suppressing oncogenesis[36]. Histone acetylation has been shown to regulate tumor suppressor gene p53, or proto-oncogene c-Myb. These indicate that histone acetylation can up- or down-regulate oncogenesis[37]. Selected cancers in relation to epigenetic alterations are listed in supplemental Table 1.

Role of miRNAs

miRNAs are a group of small, noncoding RNAs that play key roles in epigenetic regulation by controlling the translation and stability of mRNAs. They are crucial in developmental processes, apoptosis, and cell proliferation[38]. However, this regulation depends on the activities of other co-factors, DNA methylation and/or histone acetylation. The other co-factors include RNA-binding protein, CREB-binding protein or E1A binding protein p300 and Cyclic AMP response element-binding protein. This regulation indirectly inhibits or promotes mRNA expression. Notably, the role of miRNAs in oncogenesis varies depending on the mRNA they regulate and thus can be promoters or suppressors of oncogenesis[39]. However, in general, most miRNAs are under-expressed in cancer compared to normal tissues.

Role of lncRNAs

lncRNAs modulate cell proliferation, senescence, migration and apoptosis. They also interact with DNA, RNA and other proteins, and regulate gene expression, and other miRNA activities. The transcribed-ultraconserved regions are a segment of DNA and considered as a novel class of non-coding RNAs. UCRs are conserved, *i.e*., unchanged between the species. Therefore, alteration in this area is unlikely to occur due to chance, and differential expressions have been observed in several cancers[40].

Oncogenes and proto-oncogenes

Oncogenes are genes that have the potential to cause cancer and are often mutated or expressed at a high level in cancer. Proto-oncogenes are normal genes that can become oncogenes when other co-stimulating factors are present. These proto-oncogenes include *Ras, Wnt, Myc, ERK,* and *Trk*.

Ras proteins, also called small GTPase are a group of ubiquitously expressed proteins in all cell lines. Their roles are in cellular signal transduction, energy regulation, and scavenging energy sources. More than 30% of all human cancers - including 95% of pancreatic cancers and 45% of colorectal cancers - are driven by mutations of the *Ras* family of genes[12]. Activated Ras proteins are master activators of other proteins ultimately leading to cell growth, differentiation and survival. Therefore, mutation in the *Ras* gene can contribute to carcinogenesis. The most prevalent *Kras* among 3 common human proto-oncogenes was associated with pancreatic cancer. *Kras* was also strongly associated with nicotine[41], and with the receptor of advanced glycation end products[42]. These facts suggest that smoking and glucose metabolism may be risk factors for pancreatic cancer *via* the Kras pathway.

Mutations in *Wnt* genes lead to a variety of diseases including breast and prostate cancers, glioblastoma, type Ⅱ diabetes, and others[43]. Wnt commonly co-exists with embryonic processes and cell fate specification, and cell proliferation. The canonical *Wnt* pathway leads to regulation of gene transcription, while the non-canonical pathway regulates the cytoskeleton. Thus, it is plausible why the non-canonical pathway is associated with periodontitis where bone remodeling is involved[44]. However, nicotine also impact on *Wnt* signaling and potential confounding by smoking is possible[45].

Myc is a regulator gene that codes for a transcription factor and plays a role in cell cycle progression, apoptosis and cellular transformation. *Myc* regulates many genes that lead to variety of cancers including carcinoma of the cervix, colon, breast, lung and stomach.

*ERK*s are extracellular-signal-regulated kinases, such as classical mitogen-activated protein (MAP) kinases. MAP kinases are widely expressed in the regulation of cell divisions and post-mitotic functions in differentiated cells. Disruption of the *ERK* pathway is common in cancers. The role of microRNAs in carcinogenesis is summarized in supplemental Table 2.

INFLAMMATION IN ONCOGENESIS

Rudolf Virchow in the 19th century hypothesized that chronic inflammation might increase tissue proliferation. Chronic inflammatory states have many features in common with cancer: Inhibition of apoptosis (partly due to inactivation of p53); induction of angiogenesis; and the activation of humoral immune response[46]. However, other metabolic conditions also express insulin-like growth factors (IGFs) and cyclo-oxygenase (Cox)-2, both of which inhibit apoptosis[46]. IGFs are closely related to metabolic inflammation and diabetes, and elevated IGF levels were associated with breast, prostate, colorectal, and lung cancer[46]. Therefore, Virchow's theorem that chronic inflammation (implicitly from infections) causes malignant transformation is yet to be proven. Rather, inflammation can be the result of cancer biology or can be paralleling phenomena without causal link to cancer pathogenesis. The reason is because inflammation can be either tumor suppressive or tumor promoting[47].

The vast majority of somatic mutations involve some form of chronic inflammation. Up to 20% of cancers were linked with chronic infections, 30% may be traced to smoking tobacco or other inhalants such as asbestos or silica and 35% can be attributable to dietary factors[48]. Subclinical and often undetectable metabolic inflammation from obesity can be a strong risk factor for liver cancer[49]. Another type of chronic inflammation that precedes tumor development is caused by immune dysregulation and autoimmunity. The example of this is inflammatory bowel disease, which greatly increases the risk of colorectal cancer.

Universal inflammatory marker NF-κB has been implicated in oncogenesis and also featured in oral dysbiosis[33]. However, NF-κB is ubiquitously expressed and controls numerous physiological processes including cell development, differentiation, immunity, metabolism and cancer. Thus, multiple confounding is possible in NF-κB expression. The fact that type 2 diabetes patients exhibited prominent NF-κB binding after LPS challenge compared with normoglycemic controls suggests that NF-κB expression may be due to metabolic inflammation rather than LPS challenge[50].

METABOLIC INFLAMMATION AND CANCER

Metabolism controls carcinogens *via* substrate availability, energy for proliferation, and cell survival. Among the multiple risk factors for oncogenesis, dysregulated metabolism is the most common and recognizable features of cancer[51]. However, its causal relationship to carcinogenesis is incompletely defined. Recent research

revealed that a high fat diet induced intestinal dysbiosis and promoted intestinal oncogenesis in *K-rasG12D*^{Dint} mice[52]. Even more significant was the fact that cancer occurred without obesity or mucosal inflammation[52]. From the research point of view, this study proves that adjusting obesity is not sufficient to control for metabolic inflammation.

Interestingly, butyrate supplementation prevented carcinogenesis in *K-rasG12D*^{int}[52] as well as *Apc*$^{min/+}$ mice models[53], while detrimental in *Apc*$^{min/+}$*Msh2*$^{-/-}$ mice[54]. This suggests that dietary changes under certain genetic conditions can either prevent or promote oncogenesis. However, they did not observe the oral bacterium *Fusobacterium nucleatum* in the intestinal cancer region[54].

In the 1920s, Otto Warburg observed that tumor cells consumed a large amount of glucose, much more than normal cells, and converted most of it to lactic acid leading to the "Warburg effect". The Warburg effect is defined as "aerobic glycolysis" which cancer cells utilize fermentation in the presence of oxygen to rapidly convert nutrients into biomass. Highly proliferative cells need glucose to be diverted to the pentose phosphate shunt and the serine/glycine pathway to produce nucleotides, excess lipid to create new cell membranes, and amino acids for the creation of new biomass[55].

Although reactive oxygen species (ROS) were implicated in infectious inflammation, glucose metabolism also generates ROS[56]. This observation is in agreement with our report that infectious and metabolic inflammation are in a confounding relationship[17].

INFECTIONS AND CANCER

Although some bacterial infections such as *Helicobacter pylori* (*H. pylori*) infections are potential causal factors for cancers, oral infections as causative factors for cancer have not been determined. To be a causal factor, oral infections must occur before the cancer manifestation. Unfortunately, most published studies in this topic were cross-sectional studies[57] which cannot be inferred as causal association. As our knowledge on oncogenesis has expanded in recent years, new risk factors such as metabolic inflammation, *p53* mutation which involved 60% of colorectal cancers[58] and this gene affects in early stage of adenoma to cancer conversion suggesting a causal role[59]. Moreover, adenomatous polyposis coli (*APC*) gene mutations that involved some 83% of sporadic colorectal cancer[60] become critical in establishing causal factors[60,61]. Thus, we have reviewed evidence from longitudinal studies published within the past 5 years.

Longitudinal human studies on oral infections and cancer

Among the very few longitudinal studies, a population-based longitudinal study reported that serum *P. gingivalis* antibody increased the risk of orodigestive cancer mortality[62]. This study adjusted confounding minimally without controlling for alcohol consumption and the risk from *APC* gene mutation. Cancer risk factors are site specific, and combining oral, stomach, and intestinal cancers is problematic.

The second study linked the antibodies to several oral pathogens to pancreatic cancer[63]. Interestingly, the authors observed that the antibodies to the commensals were associated with lower risk of pancreatic cancer. This suggests that dysbiosis may be a more appropriate risk marker than the role of a few pathogens. Dysbiosis on the other hand, can be a marker for abnormal immunity which predisposes to cancer development[64]. Although this study adjusted for confounders reasonably well, still *APC* or *Kras* gene mutations that are highly important to pancreatic cancer were not considered. Pancreatic cancer is a basically metabolic dysfunction based disease and *Kras* gene mutations are involved in 95% of pancreatic cancers[12].

A longitudinal study that assessed periodontal treatment by insurance claims was associated with lower risk of subsequent cancers but this study did not adjust for smoking, alcohol consumption or genetics[65]. Another insurance claims study examined the relationship of periodontitis diagnosis to pancreatic cancer incidence in 12 years of follow-up. The researchers observed a significant increase in pancreatic cancer risk among age 65 or older persons diagnosed with periodontitis at baseline[64]. This study is the largest by far and controlled for confounding well although some proxies were used. A more positive aspect of this study is that other infections such as viral hepatitis, and pancreatitis were adjusted. However, genetic mutations were not adjusted. Notably, *Kras* mutations were found in 71%-95% of pancreatic cancers along with the APC mutation[66], and thus it is absolutely required to adjust these gene mutations in pancreatic cancer.

Recently, periodontitis was implicated as a causal factor for non-Hodgkin's lymphoma (NHL)[67]. However, the low immunity resulting from the outcome may incite periodontitis. Thus, it is highly likely that periodontitis may be the reflection of low immunity resulting from lymphoma itself rather than a causal factor for it as we have stipulated in our letter to the editor of the *International Journal of Cancer*[68]. Immunosuppression in NHL is biologically plausible because in non-Hodgkin's lymphoma, the circulatory system is crowded with immature lymphocytes which cannot generate strong immune responses when needed. Oral manifestations of leukemia are well-known with references dating back to 1930s and 40s[69,70]. Thus, reverse causation (periodontitis being the result of lymphoma) is possible due to long symptom-free latency[71]. This study did not adjust for the chemical exposure, a strong risk factor for lymphomas[72-75]. These longitudinal studies evaluating oral infections and oncogenesis are

Table 3 Longitudinal studies on the association of oral infections with cancer

	Design/sample size/f-u	Predictor	Outcome	Methods	Results	Comments
Ahn *et al*[62], 2012	Prospective follow-up study: (n = 105) Approximately 12 yr f-u	Serum *P. gingivalis* antibody and periodontitis status	ODC mortality	Cox proportional hazards regression analysis Controlled age, sex, smoking status, education, race/ethnicity and BMI	Periodontitis increase CRC risk (RR = 3.58, 95%CI: 1.15-11.16) Greater serum *P. gingivalis* IgG → non-significant increase in risk for ODC mortality	No adjustment of alcohol consumption and genetics Cox regression n = event number May be underpowered
Michaud[63], 2013	Nested case-control study: n = 405 cases and 416 matched controls Approximately 10 yr f-u	Plasma antibodies to 25 oral bacteria	Pancreatic cancer	Conditional logistic regression: Matched on centre, sex, follow-up time, age collection, date and time of blood collection, fasting status and use of exogenous hormones among women Additional adjustment of smoking and BMI	High antibody level to *P. gingivalis* double the risk (non-significant) → OR = 2.11 (0.97-4.59), P > 0.05 High antibody levels to commensals → 45% lower cancer risk (significant): OR = 0.55, 95%CI: 0.36-0.83, P < 0.05	No adjustment of genetics No adjustment of metabolic oncogenes, *i.e.*, *k-ras*
Hwang *et al*[65], 2014	Age, sex matched case-control (1:2), n = 116706 Approximately 13 yr f-u	Periodontal treatment by insurance claims	Death, withdrawal from the NHI system, or any cancer diagnosis	Cox proportional hazards regression Age, sex, occupation, T2D hypertension, hyperlipidemia	HR = 0.72, 95%CI: 0.68-0.76, P < 0.05	No adjustment of smoking, alcohol consumption or genetics
Chang *et al*[64], 2016	Prospective cohort study, n = 214890 Approximately 12 yr f-u	PD diagnosis by insurance claims	Censored or diagnosed with pancreatic cancer	Cox proportional hazards regression Adjusted for age, sex, diabetes, hypelipidemia, allergies, viral hepatitis, peptic ulcer, pancreatitis, COPD, and alcohol-related conditions	HR = 1.55 (1.02-2.33), P = 0.04 in the whole cohort Age ⩾ 65 (HR = 2.17, 95%CI: 1.03-5.47) Age < 65 yr (HR = 0.83, 95%CI: 0.52-1.34) Men (HR = 1.72, 95%CI: 1.01-2.93; women HR = 1.33, 95%CI: 0.69-2.55)	Proxies for smoking and alcohol consumption adjusted Viral hepatitis, gastric ulcer and pancreatitis adjustment is positive Genetics was not adjusted
Bertrand *et al*[67], 2016	Prospective cohort, 26 yr f-u, n = 51529	History of periodontitis assessed by questionnaire	Non-Hodgkin's lymphoma including CLL; SLL; diffuse large B-cell lymphomas; follicular lymphomas	Lymphoma in general has strong correlation to hereditary immune suppression and chemical usage, *i.e.*, pesticides → lymphoma is prevalent in agricultural workers	Overall NHL HR = 1.30 (95%CI: 1.11-1.51) CLL/SLL HR = 1.41 (95%CI: 1.08-1.84)	Lymphoma → lower immunity → periodontitis may be a marker for suppressed immunity Chemical exposure was not controlled Reverse causation is possible due to long asymptomatic latency

CLL: Chronic lymphocytic leukemia; SLL: Small lymphocytic lymphomas; ODC: Orodigestive cancer; f-u: Follow-up; COPD: Chronic obstructive pulmonary disease; CRC: Colorectal cancer; PD: Periodontitis.

summarized in Table 3.

Animal studies on oral infections and cancer

In an elaborate murine study, 4-nitroquinoline-1-oxide induced oral squamous cell carcinoma (OSCC) and when *F. nucleatum* and *P. gingivalis* were co-cultured with cancer cells, OSCC progressed much more rapidly. These oral pathogens were not the initiating factor but rather enhancers of cancer progression[76].

A similar experiment was conducted utilizing multiple intestinal neoplasia gene positive ($APC^{min/+}$) mice and also observed the enrichment of *Fusobacterium spp*[77]. Here "min" designates "multiple intestinal neoplasia" gene. Another study observed strong presence of *F. nucleatum* in colorectal cancer (CRC)[78]. *F. nucleatum* was reported to activate the β-catenin/adhesin pathway and invades intercellular space *via* FadA adhesin[78]. However, the initiation of CRC may still be due to genetic susceptibility as the expert speculates that *APC* gene mutation is an initiating event and the presence of *F. nucleatum* may be a consequence[79]. Therefore, we concur with the statements that if genetic damage is the "match that lights the fire", infection may be the "fuel that feeds the

flames"[80].

Additionally, CRCs are driven by *Kras* pathway which is highly dependent on glucose metabolism, obesity, and lipid metabolism. Also, other epigenetic changes such as site specific DNA hypermethylation, loss of p53, Cox-2, mutation of *Kras* and *Braf*, all transform benign colon adenoma to malignant adenocarcinoma[81].

E-cadherins interact with β-catenin and maintain epithelial integrity. They not only act as physical barrier of invasion of pathogens but also provide Wnt-signaling pathway[82]. Loss of e-cadherins preceded the appearance of malignancy[83].

E-cadherins compete with APC, a tumor suppressor gene, thus become a risk factor for CRC, for β-catenin binding[84]. The close relationship of β-catenin and APC should be noted. Thus, potential confounding is conceivable through the ubiquitous Wnt/β-catenin signaling pathway. Moreover, cellular permeability was a risk factor for colon cancer and intestinal permeability is increased in metabolic inflammation[17]. Thus, it is uncertain whether *F. nucleatum* is a cause for oncogenesis or an opportunistic commensal microorganism that exploits diminished adhesion and translocates to the cancer site.

Oral virus infections and cancer

All human herpes viruses can evade immune surveillance and suppress the immune system and thus, once infected, they can stay dormant and be reactivated under certain conditions. Among these, EBV and KSHV are recognized as oncogenic viruses[85]. EBV was persistently present in oral mucosa and detected in OSCC, and also in nasopharyngeal cancer. However, detection does not confirm their causal role in oncogenesis.

Oral HPV has been implicated in uterine and head and neck cancers[86]. HPVs promote malignancy by mutating the tumor suppressor gene p53 by their oncoproteins E6 or E7[87]. However, HPV infections are often co-infected with a more sinister Epstein-Barr virus. Also, smoking and alcohol consumption coexist with HPV and this fact suggests that the role of HPV can be as an opportunistic bystander. Several researchers claimed that HPV might be a causal factor for head and neck cancers but we did not find any longitudinal data to support the causal relationship. Most references in this area were cross-sectional studies in case-control format with very short follow-up. A prominent expert in this field quoted that the World Health Organization (WHO) determined that HPV infection was the cause for HNSCC[88]. When we verified the evidence in the WHO website, we found only several case series as evidence for the causal association of HPV and cancer. Case-series or even case-control study results are hardly sufficient evidence for causality establishment in the evidence-based medicine[89]. At the present, the existing evidence is not solid enough to establish a causal role of HPV infection in oral carcinogenesis. In a longitudinal study, Gillison *et al*[88] reported that "the seropositivity to HPV is not a marker for infection nor do HPV16 L1 antibodies protect from infection"[90]. Interestingly, the current HPV vaccination uses HPV16 L1 to induce antibodies[91]. Thus, the utility of this vaccine for HPV prevention is of questionable value. Only 1% of population have oral HPV type 16 that is found in oropharyngeal cancers[92] and this can be interpreted that 99% of HPV infections are not associated with oral malignancy. Considering the totality of evidence, we concur with the expert not associated with this particular group[91] and also with the view of the Centers for Disease Controls and prevention in that "It is unclear if having HPV alone is sufficient to cause oropharyngeal cancers, or if other factors (such as smoking or chewing tobacco) interact with HPV to cause these cancers". http://www.cdc.gov/std/hpv/stdfact-hpvandoropharyngealcancer.htm.

Many experts consider that the presence of oral bacteria in cancer tissues may be the consequence of the cancer microenvironment[79] or marker for immune dysfunction which predisposes to cancer[64]. Some microorganisms can translocate to the lesion where cancer microenvironments engender low immunity. Especially in non-Hodgkin's lymphomas that accompany generalized low immunity due to dysfunctional lymphocytes, periodontitis may be one of the manifestations of this low immunity[67]. Some measure of host immunity should be adjusted to reach an unbiased assessment of the relationship between oral infections and carcinogenesis. More importantly, a prediction model to evaluate the relative importance of each factor to carcinogenesis is necessary to prevent siphoning limited resources to minor risk factors.

CONCLUSION

Genetics, immunity epigenetics and inflammation may play major roles in carcinogenesis. Most notably, inflammation from endogenous sources (metabolic inflammation) is a strong contributor, while inflammation from exogenous infection may play a minor role in cancer development[17] with few exceptions such as *H. pylori* in gastric cancers.

Although we found some indications that oral infection may contribute to carcinogenesis, we are unable to determine whether there is unequivocal evidence that oral infections are independent cause for carcinogenesis. The reason is that the key initiating factors, the gene mutations[4] were not controlled in any studies. Ignoring APC mutation in colorectal cancers or *Ras* protein's role in pancreatic cancer will result in biased conclusion. Additionally, periodontitis is an inflammatory/immune-related disease and systemic immunity affects its manifestation.

It is, therefore, possible that low host immunity

may connect cancer and periodontitis but the causal contribution of oral infection to carcinogenesis is questionable. However, there is limited evidence that oral infections may promote the progression of cancer[76,77]. Further studies are needed to examine the role of oral infections in carcinogenesis *via* the holistic approach considering the multisystem in the whole human body.

REFERENCES

1 **Siegel R**, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin* 2011; **61**: 212-236 [PMID: 21685461 DOI: 10.3322/caac.20121]

2 **Tomasetti C**, Vogelstein B. Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science* 2015; **347**: 78-81 [PMID: 25554788 DOI: 10.1126/science.1260825]

3 **Wu S**, Powers S, Zhu W, Hannun YA. Substantial contribution of extrinsic risk factors to cancer development. *Nature* 2016; **529**: 43-47 [PMID: 26675728 DOI: 10.1038/nature16166]

4 **Alexandrov LB**, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, Bignell GR, Bolli N, Borg A, Børresen-Dale AL, Boyault S, Burkhardt B, Butler AP, Caldas C, Davies HR, Desmedt C, Eils R, Eyfjörd JE, Foekens JA, Greaves M, Hosoda F, Hutter B, Ilicic T, Imbeaud S, Imielinski M, Jäger N, Jones DT, Jones D, Knappskog S, Kool M, Lakhani SR, López-Otín C, Martin S, Munshi NC, Nakamura H, Northcott PA, Pajic M, Papaemmanuil E, Paradiso A, Pearson JV, Puente XS, Raine K, Ramakrishna M, Richardson AL, Richter J, Rosenstiel P, Schlesner M, Schumacher TN, Span PN, Teague JW, Totoki Y, Tutt AN, Valdés-Mas R, van Buuren MM, van 't Veer L, Vincent-Salomon A, Waddell N, Yates LR, Zucman-Rossi J, Futreal PA, McDermott U, Lichter P, Meyerson M, Grimmond SM, Siebert R, Campo E, Shibata T, Pfister SM, Campbell PJ, Stratton MR. Signatures of mutational processes in human cancer. *Nature* 2013; **500**: 415-421 [PMID: 23945592 DOI: 10.1038/nature12477]

5 **Soto AM**, Sonnenschein C. The tissue organization field theory of cancer: a testable replacement for the somatic mutation theory. *Bioessays* 2011; **33**: 332-340 [PMID: 21503935 DOI: 10.1002/bies.201100025]

6 **Senovilla L**, Vitale I, Martins I, Tailler M, Pailleret C, Michaud M, Galluzzi L, Adjemian S, Kepp O, Niso-Santano M, Shen S, Mariño G, Criollo A, Boilève A, Job B, Ladoire S, Ghiringhelli F, Sistigu A, Yamazaki T, Rello-Varona S, Locher C, Poirier-Colame V, Talbot M, Valent A, Berardinelli F, Antoccia A, Ciccosanti F, Fimia GM, Piacentini M, Fueyo A, Messina NL, Li M, Chan CJ, Sigl V, Pourcher G, Ruckenstuhl C, Carmona-Gutierrez D, Lazar V, Penninger JM, Madeo F, López-Otín C, Smyth MJ, Zitvogel L, Castedo M, Kroemer G. An immunosurveillance mechanism controls cancer cell ploidy. *Science* 2012; **337**: 1678-1684 [PMID: 23019653 DOI: 10.1126/science.1224922]

7 **Stratton MR**, Campbell PJ, Futreal PA. The cancer genome. *Nature* 2009; **458**: 719-724 [PMID: 19360079 DOI: 10.1038/nature07943]

8 **Rosenfeld S**. Are the somatic mutation and tissue organization field theories of carcinogenesis incompatible? *Cancer Inform* 2013; **12**: 221-229 [PMID: 24324325 DOI: 10.4137/CIN.S13013]

9 **Ptashne M**. On the use of the word 'epigenetic'. *Curr Biol* 2007; **17**: R233-R236 [PMID: 17407749 DOI: 10.1016/j.cub.2007.02.030]

10 **You JS**, Jones PA. Cancer genetics and epigenetics: two sides of the same coin? *Cancer Cell* 2012; **22**: 9-20 [PMID: 22789535 DOI: 10.1016/j.ccr.2012.06.008]

11 **Rosenfeld S**. Global consensus theorem and self-organized criticality: unifying principles for understanding self-organization, swarm intelligence and mechanisms of carcinogenesis. *Gene Regul Syst Bio* 2013; **7**: 23-39 [PMID: 23471309 DOI: 10.4137/GRSB.S10885]

12 **NIH**. Risk Factors for Cancer. [website]. 2015 Apr. Available from: URL: http://www.cancer.gov/about-cancer/causes-prevention/risk

13 **Coussens LM**, Werb Z. Inflammation and cancer. *Nature* 2002; **420**: 860-867 [PMID: 12490959 DOI: 10.1038/nature01322]

14 **Coussens LM**, Fingleton B, Matrisian LM. Matrix metalloproteinase inhibitors and cancer: trials and tribulations. *Science* 2002; **295**: 2387-2392 [PMID: 11923519 DOI: 10.1126/science.1067100]

15 **Swann JB**, Smyth MJ. Immune surveillance of tumors. *J Clin Invest* 2007; **117**: 1137-1146 [PMID: 17476343 DOI: 10.1172/JCI31405]

16 **Janket SJ**, Ackerson LK. What is passing through toll gate 4: lipids or infection? *Arch Oral Biol* 2015; **60**: 664-666 [PMID: 25645352]

17 **Janket SJ**, Javaheri H, Ackerson LK, Ayilavarapu S, Meurman JH. Oral Infections, Metabolic Inflammation, Genetics, and Cardiometabolic Diseases. *J Dent Res* 2015; **94**: 119S-127S [PMID: 25840582]

18 **Dandekar RC**, Kingaonkar AV, Dhabekar GS. Role of macrophages in malignancy. *Ann Maxillofac Surg* 2011; **1**: 150-154 [PMID: 23482819 DOI: 10.4103/2231-0746.92782]

19 **Kataki A**, Scheid P, Piet M, Marie B, Martinet N, Martinet Y, Vignaud JM. Tumor infiltrating lymphocytes and macrophages have a potential dual role in lung cancer by supporting both host-defense and tumor progression. *J Lab Clin Med* 2002; **140**: 320-328 [PMID: 12434133 DOI: 10.1067/mlc.2002.128317]

20 **Mantovani A**, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol* 2004; **25**: 677-686 [PMID: 15530839 DOI: 10.1016/j.it.2004.09.015]

21 **Raggi C**, Mousa HS, Correnti M, Sica A, Invernizzi P. Cancer stem cells and tumor-associated macrophages: a roadmap for multitargeting strategies. *Oncogene* 2016; **35**: 671-682 [PMID: 25961921 DOI: 10.1038/onc.2015.132]

22 **Mantovani A**, Allavena P. The interaction of anticancer therapies with tumor-associated macrophages. *J Exp Med* 2015; **212**: 435-445 [PMID: 25753580 DOI: 10.1084/jem.20150295]

23 **Page DB**, Postow MA, Callahan MK, Allison JP, Wolchok JD. Immune modulation in cancer with antibodies. *Annu Rev Med* 2014; **65**: 185-202 [PMID: 24188664 DOI: 10.1146/annurev-med-092012-112807]

24 **Groeger S**, Domann E, Gonzales JR, Chakraborty T, Meyle J. B7-H1 and B7-DC receptors of oral squamous carcinoma cells are upregulated by Porphyromonas gingivalis. *Immunobiology* 2011; **216**: 1302-1310 [PMID: 21723642 DOI: 10.1016/j.imbio.2011.05.005]

25 **Allison JP**. Immune Checkpoint Blockade in Cancer Therapy: The 2015 Lasker-DeBakey Clinical Medical Research Award. *JAMA* 2015; **314**: 1113-1114 [PMID: 26348357 DOI: 10.1001/jama.2015.11929]

26 **Mittal D**, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. *Curr Opin Immunol* 2014; **27**: 16-25 [PMID: 24531241 DOI: 10.1016/j.coi.2014.01.004]

27 **Sharma P**, Allison JP. The future of immune checkpoint therapy. *Science* 2015; **348**: 56-61 [PMID: 25838373 DOI: 10.1126/science.aaa8172]

28 **Gordon JA**, Stein JL, Westendorf JJ, van Wijnen AJ. Chromatin modifiers and histone modifications in bone formation, regeneration, and therapeutic intervention for bone-related disease. *Bone* 2015; **81**: 739-745 [PMID: 25836763 DOI: 10.1016/j.bone.2015.03.011]

29 **Baylin SB**, Jones PA. A decade of exploring the cancer epigenome - biological and translational implications. *Nat Rev Cancer* 2011; **11**: 726-734 [PMID: 21941284 DOI: 10.1038/nrc3130]

30 **Barros SP**, Offenbacher S. Modifiable risk factors in periodontal disease: epigenetic regulation of gene expression in the inflammatory response. *Periodontol 2000* 2014; **64**: 95-110 [PMID: 24320958 DOI: 10.1111/prd.12000]

31 **Larsson L**, Castilho RM, Giannobile WV. Epigenetics and its

role in periodontal diseases: a state-of-the-art review. *J Periodontol* 2015; **86**: 556-568 [PMID: 25415244 DOI: 10.1902/jop.2014.140559]
32 **Jones PA**. Functions of DNA methylation: islands, start sites, gene bodies and beyond. *Nat Rev Genet* 2012; **13**: 484-492 [PMID: 22641018 DOI: 10.1038/nrg3230]
33 **Martins MD**, Jiao Y, Larsson L, Almeida LO, Garaicoa-Pazmino C, Le JM, Squarize CH, Inohara N, Giannobile WV, Castilho RM. Epigenetic Modifications of Histones in Periodontal Disease. *J Dent Res* 2016; **95**: 215-222 [PMID: 26496800]
34 **Li A**, Omura N, Hong SM, Goggins M. Pancreatic cancer DNMT1 expression and sensitivity to DNMT1 inhibitors. *Cancer Biol Ther* 2010; **9**: 321-329 [PMID: 20234167 DOI: 10.4161/cbt.9.4.10750]
35 **Lillycrop KA**, Slater-Jefferies JL, Hanson MA, Godfrey KM, Jackson AA, Burdge GC. Induction of altered epigenetic regulation of the hepatic glucocorticoid receptor in the offspring of rats fed a protein-restricted diet during pregnancy suggests that reduced DNA methyltransferase-1 expression is involved in impaired DNA methylation and changes in histone modifications. *Br J Nutr* 2007; **97**: 1064-1073 [PMID: 17433129 DOI: 10.1017/S000711450769196X]
36 **Shahbazian MD**, Grunstein M. Functions of site-specific histone acetylation and deacetylation. *Annu Rev Biochem* 2007; **76**: 75-100 [PMID: 17362198 DOI: 10.1146/annurev.biochem.76.052705.162114]
37 **Archer SY**, Hodin RA. Histone acetylation and cancer. *Curr Opin Genet Dev* 1999; **9**: 171-174 [PMID: 10322142 DOI: 10.1016/S0959-437X(99)80026-4]
38 **Ling H**, Fabbri M, Calin GA. MicroRNAs and other non-coding RNAs as targets for anticancer drug development. *Nat Rev Drug Discov* 2013; **12**: 847-865 [PMID: 24172333 DOI: 10.1038/nrd4140]
39 **Lee YS**, Dutta A. MicroRNAs in cancer. *Annu Rev Pathol* 2009; **4**: 199-227 [PMID: 18817506 DOI: 10.1146/annurev.pathol.4.110807.092222]
40 **Goto K**, Ishikawa S, Honma R, Tanimoto K, Sakamoto N, Sentani K, Oue N, Teishima J, Matsubara A, Yasui W. The transcribed-ultraconserved regions in prostate and gastric cancer: DNA hypermethylation and microRNA-associated regulation. *Oncogene* 2016; **35**: 3598-3606 [PMID: 26640143]
41 **Hermann PC**, Sancho P, Cañamero M, Martinelli P, Madriles F, Michl P, Gress T, de Pascual R, Gandia L, Guerra C, Barbacid M, Wagner M, Vieira CR, Aicher A, Real FX, Sainz B, Heeschen C. Nicotine promotes initiation and progression of KRAS-induced pancreatic cancer via Gata6-dependent dedifferentiation of acinar cells in mice. *Gastroenterology* 2014; **147**: 1119-33.e4 [PMID: 25127677 DOI: 10.1053/j.gastro.2014.08.002]
42 **Kang R**, Hou W, Zhang Q, Chen R, Lee YJ, Bartlett DL, Lotze MT, Tang D, Zeh HJ. RAGE is essential for oncogenic KRAS-mediated hypoxic signaling in pancreatic cancer. *Cell Death Dis* 2014; **5**: e1480 [PMID: 25341034 DOI: 10.1038/cddis.2014.445]
43 **Logan CY**, Nusse R. The Wnt signaling pathway in development and disease. *Annu Rev Cell Dev Biol* 2004; **20**: 781-810 [PMID: 15473860 DOI: 10.1146/annurev.cellbio.20.010403.113126]
44 **Zhou Y**, Sztukowska M, Wang Q, Inaba H, Potempa J, Scott DA, Wang H, Lamont RJ. Noncanonical activation of β-catenin by Porphyromonas gingivalis. *Infect Immun* 2015; **83**: 3195-3203 [PMID: 26034209 DOI: 10.1128/IAI.00302-15]
45 **Zhou Z**, Li B, Dong Z, Liu F, Zhang Y, Yu Y, Shang F, Wu L, Wang X, Jin Y. Nicotine deteriorates the osteogenic differentiation of periodontal ligament stem cells through α7 nicotinic acetylcholine receptor regulating Wnt pathway. *PLoS One* 2013; **8**: e83102 [PMID: 24376645 DOI: 10.1371/journal.pone.0083102]
46 **O'Byrne KJ**, Dalgleish AG. Infection and cancer. *Lancet* 2001; **358**: 156 [PMID: 11474502]
47 **Grivennikov SI**, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* 2010; **140**: 883-899 [PMID: 20303878 DOI: 10.1016/j.cell.2010.01.025]
48 **Aggarwal BB**, Vijayalekshmi RV, Sung B. Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. *Clin Cancer Res* 2009; **15**: 425-430 [PMID: 19147746]
49 **Park EJ**, Lee JH, Yu GY, He G, Ali SR, Holzer RG, Osterreicher CH, Takahashi H, Karin M. Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. *Cell* 2010; **140**: 197-208 [PMID: 20141834 DOI: 10.1016/j.cell.2009.12.052]
50 **Andreasen AS**, Kelly M, Berg RM, Møller K, Pedersen BK. Type 2 diabetes is associated with altered NF-κB DNA binding activity, JNK phosphorylation, and AMPK phosphorylation in skeletal muscle after LPS. *PLoS One* 2011; **6**: e23999 [PMID: 21931634 DOI: 10.1371/journal.pone.0023999]
51 **Robey RB**, Weisz J, Kuemmerle NB, Salzberg AC, Berg A, Brown DG, Kubik L, Palorini R, Al-Mulla F, Al-Temaimi R, Colacci A, Mondello C, Raju J, Woodrick J, Scovassi AI, Singh N, Vaccari M, Roy R, Forte S, Memeo L, Salem HK, Amedei A, Hamid RA, Williams GP, Lowe L, Meyer J, Martin FL, Bisson WH, Chiaradonna F, Ryan EP. Metabolic reprogramming and dysregulated metabolism: cause, consequence and/or enabler of environmental carcinogenesis? *Carcinogenesis* 2015; **36** Suppl 1: S203-S231 [PMID: 26106140 DOI: 10.1093/carcin/bgv037]
52 **Schulz MD**, Atay C, Heringer J, Romrig FK, Schwitalla S, Aydin B, Ziegler PK, Varga J, Reindl W, Pommerenke C, Salinas-Riester G, Böck A, Alpert C, Blaut M, Polson SC, Brandl L, Kirchner T, Greten FR, Polson SW, Arkan MC. High-fat-diet-mediated dysbiosis promotes intestinal carcinogenesis independently of obesity. *Nature* 2014; **514**: 508-512 [PMID: 25174708 DOI: 10.1038/nature13398]
53 **Singh N**, Gurav A, Sivaprakasam S, Brady E, Padia R, Shi H, Thangaraju M, Prasad PD, Manicassamy S, Munn DH, Lee JR, Offermanns S, Ganapathy V. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. *Immunity* 2014; **40**: 128-139 [PMID: 24412617 DOI: 10.1016/j.immuni.2013.12.007]
54 **Belcheva A**, Irrazabal T, Robertson SJ, Streutker C, Maughan H, Rubino S, Moriyama EH, Copeland JK, Kumar S, Green B, Geddes K, Pezo RC, Navarre WW, Milosevic M, Wilson BC, Girardin SE, Wolever TM, Edelmann W, Guttman DS, Philpott DJ, Martin A. Gut microbial metabolism drives transformation of MSH2-deficient colon epithelial cells. *Cell* 2014; **158**: 288-299 [PMID: 25036629 DOI: 10.1016/j.cell.2014.04.051]
55 **Wu W**, Zhao S. Metabolic changes in cancer: beyond the Warburg effect. *Acta Biochim Biophys Sin* (Shanghai) 2013; **45**: 18-26 [PMID: 23257292 DOI: 10.1093/abbs/gms104]
56 **Wallace DC**. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. *Annu Rev Genet* 2005; **39**: 359-407 [PMID: 16285865 DOI: 10.1146/annurev.genet.39.110304.095751]
57 **Meurman JH**, Bascones-Martinez A. Are oral and dental diseases linked to cancer? *Oral Dis* 2011; **17**: 779-784 [PMID: 21819493 DOI: 10.1111/j.1601-0825.2011.01837.x]
58 **Popat S**, Chen Z, Zhao D, Pan H, Hearle N, Chandler I, Shao Y, Aherne W, Houlston R. A prospective, blinded analysis of thymidylate synthase and p53 expression as prognostic markers in the adjuvant treatment of colorectal cancer. *Ann Oncol* 2006; **17**: 1810-1817 [PMID: 16971666]
59 **Armaghany T**, Wilson JD, Chu Q, Mills G. Genetic alterations in colorectal cancer. *Gastrointest Cancer Res* 2012; **5**: 19-27 [PMID: 22574233]
60 **Rowan AJ**, Lamlum H, Ilyas M, Wheeler J, Straub J, Papadopoulou A, Bicknell D, Bodmer WF, Tomlinson IP. APC mutations in sporadic colorectal tumors: A mutational "hotspot" and interdependence of the "two hits". *Proc Natl Acad Sci USA* 2000; **97**: 3352-3357 [PMID: 10737795 DOI: 10.1073/pnas.97.7.3352]
61 **Samowitz WS**, Slattery ML, Sweeney C, Herrick J, Wolff RK, Albertsen H. APC mutations and other genetic and epigenetic changes in colon cancer. *Mol Cancer Res* 2007; **5**: 165-170 [PMID: 17293392 DOI: 10.1158/1541-7786.MCR-06-0398]
62 **Ahn J**, Segers S, Hayes RB. Periodontal disease, Porphyromonas gingivalis serum antibody levels and orodigestive cancer mortality. *Carcinogenesis* 2012; **33**: 1055-1058 [PMID: 22367402 DOI:

10.1093/carcin/bgs112]
63 **Michaud DS**, Izard J, Wilhelm-Benartzi CS, You DH, Grote VA, Tjønneland A, Dahm CC, Overvad K, Jenab M, Fedirko V, Boutron-Ruault MC, Clavel-Chapelon F, Racine A, Kaaks R, Boeing H, Foerster J, Trichopoulou A, Lagiou P, Trichopoulos D, Sacerdote C, Sieri S, Palli D, Tumino R, Panico S, Siersema PD, Peeters PH, Lund E, Barricarte A, Huerta JM, Molina-Montes E, Dorronsoro M, Quirós JR, Duell EJ, Ye W, Sund M, Lindkvist B, Johansen D, Khaw KT, Wareham N, Travis RC, Vineis P, Bueno-de-Mesquita HB, Riboli E. Plasma antibodies to oral bacteria and risk of pancreatic cancer in a large European prospective cohort study. *Gut* 2013; **62**: 1764-1770 [PMID: 22990306 DOI: 10.1136/gutjnl-2012-303006]
64 **Chang JS**, Tsai CR, Chen LT, Shan YS. Investigating the Association Between Periodontal Disease and Risk of Pancreatic Cancer. *Pancreas* 2016; **45**: 134-141 [PMID: 26474422 DOI: 10.1097/MPA.0000000000000419]
65 **Hwang IM**, Sun LM, Lin CL, Lee CF, Kao CH. Periodontal disease with treatment reduces subsequent cancer risks. *QJM* 2014; **107**: 805-812 [PMID: 24722845]
66 **Flanders TY**, Foulkes WD. Pancreatic adenocarcinoma: epidemiology and genetics. *J Med Genet* 1996; **33**: 889-898 [PMID: 8950667 DOI: 10.1136/jmg.33.11.889]
67 **Bertrand KA**, Shingala J, Evens A, Birmann BM, Giovannucci E, Michaud DS. Periodontal disease and risk of non-Hodgkin lymphoma in the Health Professionals Follow-Up Study. *Int J Cancer* 2017; **140**: 1020-1026 [PMID: 27861844]
68 **Janket SJ**, Ackerson LK, Meurman JH. Potential reverse causation? *Int J Cancer* 2017 **140**: 2168 [PMID: 28124450]
69 **Moloney WC**. Clinical Significance of Oral Lesions in Acute Leukemia. *New Engl J Med* 1940; **222**: 577-579 [DOI: 10.1056/NEJM194004042221404]
70 **Forkner CE**. Clinical and pathologic differentiation of the acute leukemias: With special reference to acute monocytic leukemia. *Arch Intern Med* 1934; **53**: 1-34 [DOI: 10.1001/archinte.1934.00160070004001]
71 **Kaaks R**, Sookthai D, Łuczyńska A, Oakes CC, Becker S, Johnson T, Johansson A, Melin B, Sjöberg K, Trichopoulos D, Trichopoulou A, Lagiou P, Mattiello A, Tumino R, Masala G, Agnoli C, Boeing H, Aleksandrova K, Brennan P, Franceschi S, Roulland S, Casabonne D, de Sanjose S, Sánchez MJ, Huerta JM, Ardanaz E, Sala N, Overvad K, Tjønneland A, Halkjær J, Weiderpass E, Bueno-de-Mesquita HB, Vermeulen R, Peeters PH, Vineis P, Kelly RS, Khaw KT, Travis RC, Key TJ, Riboli E, Nieters A. Lag times between lymphoproliferative disorder and clinical diagnosis of chronic lymphocytic leukemia: a prospective analysis using plasma soluble CD23. *Cancer Epidemiol Biomarkers Prev* 2015; **24**: 538-545 [PMID: 25542829 DOI: 10.1158/1055-9965.EPI-14-1107]
72 **Karunanayake CP**, Dosman JA, Pahwa P. Non-hodgkin's lymphoma and work in agriculture: Results of a two case-control studies in Saskatchewan, Canada. *Indian J Occup Environ Med* 2013; **17**: 114-121 [PMID: 24872670 DOI: 10.4103/0019-5278.130860]
73 **Miligi L**, Costantini AS, Bolejack V, Veraldi A, Benvenuti A, Nanni O, Ramazzotti V, Tumino R, Stagnaro E, Rodella S, Fontana A, Vindigni C, Vineis P. Non-Hodgkin's lymphoma, leukemia, and exposures in agriculture: results from the Italian multicenter case-control study. *Am J Ind Med* 2003; **44**: 627-636 [PMID: 14635239 DOI: 10.1002/ajim.10289]
74 **Pearce NE**, Smith AH, Fisher DO. Malignant lymphoma and multiple myeloma linked with agricultural occupations in a New Zealand Cancer Registry-based study. *Am J Epidemiol* 1985; **121**: 225-237 [PMID: 4014117 DOI: 10.1093/oxfordjournals.aje.a113993]
75 **Schinasi L**, Leon ME. Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2014; **11**: 4449-4527 [PMID: 24762670 DOI: 10.3390/ijerph110404449]
76 **Binder Gallimidi A**, Fischman S, Revach B, Bulvik R, Maliutina A, Rubinstein AM, Nussbaum G, Elkin M. Periodontal pathogens Porphyromonas gingivalis and Fusobacterium nucleatum promote tumor progression in an oral-specific chemical carcinogenesis model. *Oncotarget* 2015; **6**: 22613-22623 [PMID: 26158901 DOI: 10.18632/oncotarget.4209]
77 **Kostic AD**, Chun E, Robertson L, Glickman JN, Gallini CA, Michaud M, Clancy TE, Chung DC, Lochhead P, Hold GL, El-Omar EM, Brenner D, Fuchs CS, Meyerson M, Garrett WS. Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. *Cell Host Microbe* 2013; **14**: 207-215 [PMID: 23954159 DOI: 10.1016/j.chom.2013.07.007]
78 **Rubinstein MR**, Wang X, Liu W, Hao Y, Cai G, Han YW. Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadA adhesin. *Cell Host Microbe* 2013; **14**: 195-206 [PMID: 23954158 DOI: 10.1016/j.chom.2013.07.012]
79 **Keku TO**, McCoy AN, Azcarate-Peril AM. Fusobacterium spp. and colorectal cancer: cause or consequence? *Trends Microbiol* 2013; **21**: 506-508 [PMID: 24029382 DOI: 10.1016/j.tim.2013.08.004]
80 **Balkwill F**, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 2001; **357**: 539-545 [PMID: 11229684 DOI: 10.1016/S0140-6736(00)04046-0]
81 **Yamada Y**, Mori H. Multistep carcinogenesis of the colon in Apc(Min/+) mouse. *Cancer Sci* 2007; **98**: 6-10 [PMID: 17052257 DOI: 10.1111/j.1349-7006.2006.00348.x]
82 **Tian X**, Liu Z, Niu B, Zhang J, Tan TK, Lee SR, Zhao Y, Harris DC, Zheng G. E-cadherin/β-catenin complex and the epithelial barrier. *J Biomed Biotechnol* 2011; **2011**: 567305 [PMID: 22007144]
83 **Strumane K**, Berx G, Van Roy F. Cadherins in cancer. *Handb Exp Pharmacol* 2004; (**165**): 69-103 [PMID: 20455091 DOI: 10.1007/978-3-540-68170-0_4]
84 **Hülsken J**, Birchmeier W, Behrens J. E-cadherin and APC compete for the interaction with beta-catenin and the cytoskeleton. *J Cell Biol* 1994; **127**: 2061-2069 [PMID: 7806582 DOI: 10.1083/jcb.127.6.2061]
85 **Alibek K**, Baiken Y, Kakpenova A, Mussabekova A, Zhussupbekova S, Akan M, Sultankulov B. Implication of human herpesviruses in oncogenesis through immune evasion and supression. *Infect Agent Cancer* 2014; **9**: 3 [PMID: 24438207 DOI: 10.1186/1750-9378-9-3]
86 **Michaud DS**, Langevin SM, Eliot M, Nelson HH, Pawlita M, McClean MD, Kelsey KT. High-risk HPV types and head and neck cancer. *Int J Cancer* 2014; **135**: 1653-1661 [PMID: 24615247]
87 **Paquette RL**, Lee YY, Wilczynski SP, Karmakar A, Kizaki M, Miller CW, Koeffler HP. Mutations of p53 and human papillomavirus infection in cervical carcinoma. *Cancer* 1993; **72**: 1272-1280 [PMID: 8393371 DOI: 10.1002/1097-0142(19930815)72: 4<1272::AID-CNCR2820720420>3.0.CO;2-Q]
88 **Gillison ML**, Castellsagué X, Chaturvedi A, Goodman MT, Snijders P, Tommasino M, Arbyn M, Franceschi S. Eurogin Roadmap: comparative epidemiology of HPV infection and associated cancers of the head and neck and cervix. *Int J Cancer* 2014; **134**: 497-507 [PMID: 23568556]
89 **Sackett DL**, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine. How to practice and teach EBM. London: Churchill-Livingstone, 1997
90 **Beachler DC**, Viscidi R, Sugar EA, Minkoff H, Strickler HD, Cranston RD, Wiley DJ, Jacobson LP, Weber KM, Margolick JB, Reddy S, Gillison ML, D'Souza G. A longitudinal study of human papillomavirus 16 L1, e6, and e7 seropositivity and oral human papillomavirus 16 infection. *Sex Transm Dis* 2015; **42**: 93-97 [PMID: 25585068 DOI: 10.1097/OLQ.0000000000000236]
91 **Sok JC**, Grandis JR. Genetic screening for oral human papillomavirus infections and cancers of the head and neck. *Clin Cancer Res* 2008; **14**: 6723-6724 [PMID: 18980962]
92 **CDC**. Human Papillomavirus (HPV). Facts and Brochures 2016; Web information. Accessed Dec. 5, 2016
93 **Zacharski LR**, Sukhatme VP. Coley's toxin revisited: immuno-

therapy or plasminogen activator therapy of cancer? *J Thromb Haemost* 2005; **3**: 424-427 [PMID: 15748226]
94 **Hoffman RM**. Future of Bacterial Therapy of Cancer. *Methods Mol Biol* 2016; **1409**: 177-184 [PMID: 26846811 DOI: 10.1007/978-1-4939-3515-4_15]
95 **Orange M**, Reuter U, Hobohm U. Coley's Lessons Remembered: Augmenting Mistletoe Therapy. *Integr Cancer Ther* 2016; **15**: 502-511 [PMID: 27207233 DOI: 10.1177/1534735416649916]

P- Reviewer: Invernizzi P, Popp C **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Li D

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com