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Review Article

Oral hygiene might prevent cancer

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Abstract

Many evidences support that species from the Human Oral Microbiome Database such as *Fusobacterium nucleatum* or *Bacteroides*, linked previously to periodontitis and appendicitis, play a role in colorectal cancer (CRC), including metastasis. These typically oral species are invasive anaerobes that form biofilms in their virulent state.

Aspirin (a NSAID) has been recently included into routine CRC prevention rationale. NSAIDs can prevent the growth of neoplastic lesions by inhibiting COX enzymes and another set of recently identified COX-independent targets, which include the WNT, AMPK and MTOR signaling pathways, the crosstalk between nucleoli and NF- κ B transcriptional activity in apoptosis, and the biochemistry of platelets. These are signaling pathways related to tumor-promoting inflammation. In this process, pathogens or simple deregulation of the microbiota play an important role in CRC. Aspirin and other NSAIDs are efficient inhibitors of biofilm formation and able to control periodontitis development preventing inflammation related to the microbiota of the gingival tissue, so its seems plausible to include this pathway in the mechanisms that aspirin uses to prevent CRC.

We propose arguments suggesting that current oral hygiene methods and other future developments against periodontitis might prevent CRC and probably other cancers, alone or in combination with other options; and that the

multidisciplinary studies needed to prove this hypothesis might be relevant for cancer prevention.

Keywords: Microbiology, Cancer research, Evidence-based medicine, Dentistry

1. Introduction

1.1. Inflammation and immunity in cancer

Accumulation of mutations in genes encoding either homeostatic regulators or DNA mismatch-repair factors, predominantly in stem cells becoming CSCs (cancer stem cells) is the leading event in carcinogenesis [1, 2]. The crucial role of the immune system in this process, however, didn't come into worldwide attention until Hanahan & Weinberg's update of their "Hallmarks of Cancer" in 2011 [3]. These Hallmarks focused on immunosuppression, a better-known mechanism, on one hand but also in inflammation as an enabling characteristic of tumor growth [4].

Inflammation and immune system are activated to eliminate pathogens and non-self molecules, or to control at least their dissemination or systemic colonization of the organism, but the same physiological responses induce repair mechanisms that recover the function and integrity of tissues in an organ with tumor [5]. Moreover, the inflammation and immunitary cellular infiltrates responsible for tumor initiation and early progression are the same that can destroy the tumors before immunosuppression [6, 7]. Therefore, both hallmarks are two sides of the same coin.

In cancer, there are many possible origins for the inflammatory response. The inflammation is called **intrinsic** when the mechanisms driving the cell transformation and cancer initiation, overexpression of oncogenes (such as Ras, Myc, Src, or RET) and microRNAs (such as mi-R155), damage and mutation of DNA, and reactive oxygen species (ROS) production in mitochondria, also activate a pro-inflammatory program (the production of chemokines, interferons (IFNs) and tissue rearranging enzymes) in the proper altered cell [4, 5, 6]. **Extrinsic** inflammation is mediated, by contrast, by infiltrating immune cells [4, 5, 6]. Again DNA or mitochondrial damage, oncogene activation, or endoplasmic reticulum (ER) stress and oxidative damage of the altered cell, in addition to the many signals of cellular stress generated by the damage of the malignant cell-surrounding tissue (because of mechanical, chemical or irradiation causes, or genetic syndromes, hypoxia, the excessive temperature, or nutrients, or by senescence), serve to activate that infiltration.

Chronic inflammation affects all phases of carcinogenesis. In a feedback loop, by the generation of mutations, modifications of functional proteins or epigenetic mechanisms, it drives cell transformation, particularly when a stem cell is affected and become CSCs [3, 4, 8, 9]. At the same time, more hematopoietic inflammatory cells are recruited on the developing cancer. The leukocyte infiltrate includes neutrophils, dendritic cells, macrophages and lymphocytes, all of them capable of secreting those cytokines, ROS,

membrane perforating agents, growth factors and cellular products that contribute to the inflammatory milieu present in the environment of a developing tumor, favoring the tumor growth and, later, dissemination of the transformed cells [5, 10, 11].

1.2. Molecular mechanism of inflammation

The immune cells recruited to the tumor express multiple specialized families of pattern recognition receptors (PRRs) located at the plasma membrane, within intracellular vesicles, and in the cytosol. The most known are the Toll-like receptors (TLRs), NLRs (from Nod, nucleotide binding oligomerization domain, -like receptors), PYHIN (pyrin and HIN domain) receptors, C-type lectin receptors, RLRs (RIG-I, retinoic acid inducible gene-I, -like receptors), the oligoadenylate synthase (OAS) -like receptors, the related protein cyclic GMP-AMP synthase (cGAS), and DNA sensors such as STING (stimulator of interferon gene).

Many of them assemble to form signaling complexes, including *inflammasomes* initiated by NLR and PYHIN receptors and related to cellular oxidative stress, the *myddosomes* initiated by TLRs and the Interleukin-1 receptor (IL-1R) involving among others the MyD88 protein, and the mitochondrial antiviral signaling protein (MAVS) CARD filament initiated by RIG-I [10,12].

To note, these “innate receptors”, at least TLR 2 and 4 and NLRP3, have been recently identified also in the proper tumorigenic altered cells or in metabolic tissues, adipocytes, myocytes, liver or pancreas (see below how systemic metabolic alterations such as obesity or diabetes also cause inflammation) [13, 14] in what may represent feedback loops.

These receptors are very promiscuous by definition, i.e. one particular or a very similar ligand may bind to different receptors in the same or in a different cell. Therefore, they identify DAMPS (**damage-associated molecular patterns**) as those endogenous components released from cells damaged by molecular stress [10, 11, 12], but they were first identified as receptors of PAMPs (**pathogen-associated molecular patterns**) or receptors that identify components from microbial pathogens, this fact of particular interest for later content of the review. Recent evidence indicate that the major DAMP driving host antitumor immune responses is tumor-derived DNA, sensed by the STING pathway in a certain population of intratumoral DCs, driving the production of type I IFNs and the resulting downstream T cell response (reviewed in [15]).

The same signal transduction pathway, adaptor protein MyD88, is shared by many of these receptors. Although in rodent models, MyD88 has shown a protective role in the development of colonic tumors, MyD88 innate immune signaling and specific micro-RNAs mechanistically control CRC chemoresistance (see next subheading). Likewise, the same inflammatory mediators induce the transcription factors nuclear factor- κ B (NF- κ B) and signal transducer and activator of transcription-3 (STAT-3) [1,8-16].

The first one seems particularly relevant to gastrointestinal cancer development [5] and, in fact, NF- κ B signaling pathway has been identified as a COX-independent target of NSAIDs (as reviewed later). STAT-3 of tumor, stromal and immune cells is activated by many of factors released by the tumor and tumor stroma, for example VEGF, interleukin-6 (IL-6), IL-10, IL-11, or IL-23, are transcriptionally regulated by STAT-3 regulates transcriptionally several of these cytokines generating a positive feedback loop [17]. In addition to the carcinogenesis mentioned above, they also allow the tumor to progress and metastasize by establishing a tumoral microenvironment (for example, angiogenesis), including the immunosuppressive mechanisms that prevent the effective immune surveillance.

Finally, it must be emphasized that all these inflammatory mechanisms also affect the response to therapy [1, 15, 18].

1.3. Gut microbiota and CRC

As IBD patients —with Crohn's disease or ulcerative colitis— have a several-fold increased susceptibility to CRC principally, they were considered typical examples of colitis-associated cancer (CAC), the first inflammation-related cancer [19, 20]. In this cancer, the intestinal epithelial barrier already includes in the healthy individual complex molecular and cellular interactions of **commensal microbiota** with the epithelial, mesenchymal and immune cells to achieve intestinal homeostasis, regeneration, and healing (reviewed in [21]). The gut microbiota composition can be altered by the presence of a specific bacterial species or modulated by an environmental change. The presence of different natural mutagens and carcinogens, of a metabolism provided by the commensal flora that requires or can be regulated by a specific enzymatic activity, or the straightforward interaction of the bacteria or their products with those innate receptors or sensors described above, all can generate either pro- or anti-inflammatory effects (reviewed in [11, 18]). At the beginning of the millennium the first experimental CAC models mimicking human CRC in rodents clearly established that immune cells, cytokines and the STAT-3 and NF- κ B transduction pathways all participate in the induction of inflammatory colitis (revs [8, 10, 11, 12]).

The IBD patients also show increased susceptibility to lymphomas/leukemias and hepatocarcinomas among other tumors, which suggests that the pathological intestinal inflammation triggered by the commensal microbiota is responsible for the local tumor-promoting effects but also, through the immune system, to have additional deep systemic effects [11, 18, 21]. In addition, later on the text, reviewed data suggest new roles for the microbiota, for example in CRC metastasis.

Likewise, most of the known main risk factors for CRC, obesity, lack of exercise, fat-rich diets, use of alcohol and tobacco [8, 22], are related with nutrition, being

environmental agents that can alter the commensal microbiota [7, 11, 13, 14, 15, 16]. As the wide geographical variation in the incidence of CRC are lost in migrating populations within one generation, it is likely that these risk factors are responsible of CRC in the host populations [22, 23].

Two enterobacterial species, *Klebsiella pneumoniae* and *Proteus mirabilis*, participated in the development of colitis and cancer in TRUC (immunodeficient *Tbet*^{-/-} and *Rag2*^{-/-} ulcerative colitis) mice [24, 25], however, they didn't induce colitis alone but modify either the healthy gut microbiota composition or its physiology, acting in synergy to activate colon inflammation.

Actually, another fact suggesting the role of the commensal flora in CRC is that germfree animals [26], or treated with mildly colitogenic bacterium *Bacteroides vulgatus* (the azoxymethane (AOM)-treated *Il10*^{-/-} model) [27], do not develop tumors. *Helicobacter hepaticus* infection of the gut enhanced small intestine and colon cancer in APC^{min/+} mice, but also mammary adenocarcinoma [28] or hepatocarcinomas [29], thus showing systemic tumor-promoting effects. Likewise, infection with *Helicobacter pylori* in humans is an example that a single bacterial species can trigger carcinogenesis, in this case gastric cancer [30].

Other pathogenic species identified while elucidating molecular mechanisms affected by the microbiota were the enteropathogenic *Bacteroides fragilis* (activated WNT and NF-κB signalling pathways on the carcinogenic cells) and *Escherichia coli*, also associated with increased risk of CRC (through actions that down-regulate mismatch-repair genes, at least in vitro [11, 12, 13, 14, 15, 16, 17, 31, 32]). This enteric microbiota also influences the T helper 17 (Th17) response [33, 34] and APC, in particular dendritic cells (DCs), activation [24].

More recently in *Nlrp6*^{-/-} mice the expansion of other anaerobic genus of bacterial phyla *Bacteroidetes* (like *Bacteroides*), *Prevotellaceae* (traditionally related to periodontal disease), and *TM7* (*Saccharibacteria*, interestingly, recently cultured from the human oral cavity) in the fecal microbiota correlated with susceptibility to colitis [35, 36]. Therefore, at least the NLRP6 receptor of the inflammasome in the innate system [10, 12] also regulates colonic microbial ecology.

However, although IBDs are the main risk factor for CRC, the relative increased risk for colorectal cancer in these patients is only threefold with respect to the control population, the tumors are generated after many years of intestinal pathology, and the cumulative lifetime risk is 18% [19, 20], i.e. most CRCs are not related to any pre-existing obvious intestinal inflammatory disease.

2. Main text

2.1. Gut microbiota of oral origin and biofilms in CRC

In parallel, high-throughput DNA sequencing developments ignited the identification of microbiota that affected the progression of CRC, not only in the experimental animal models mentioned above [37] but also in humans (in biopsies or stool). The marked over-representation of *Fusobacterium nucleatum* sequences in CRC tumors relative to control specimens was a striking discovery: Fusobacteria are rare constituents of the fecal microbiota, but had been cultured previously from biopsies of inflamed gut mucosa [21, 38], and *F. nucleatum* in particular is an invasive anaerobe that had been linked previously to periodontitis and appendicitis, but not to cancer.

This and the other anaerobic species of the same or similar genera including *Bacteroides*, or typically oral species such as some *Selenomonas*, *Prevotella*, and *Parvimonas micra* and *Peptostreptococcus stomatis*, some mentioned in the previous subheadings, are species included in the Human Oral Microbiome Database and also found in the gut microbiota in a significant percentage of CRC, supporting a role for the aggregate of them in CRC [39, 40, 41], although no microbial feature was universally present in the tumors. This story is very similar to the role that bacteria are playing in the pathogenesis of autoimmune rheumatoid arthritis, opening the door to the study of auto-antibodies against these bacteria both for diagnostic uses and mechanistical studies [42].

Interestingly, these are bacteria capable of forming biofilms. Biofilm structures are a consistent feature of right-sided (proximal) (although not left-sided, distal) CRC. They are constituted by symbionts of *Bacteroides fragilis* and other mentioned oral pathogens, having tumorigenesis capacity in the mucus layer of the gut [41] by disrupting the normal mucosal barrier, changing the tissue homeostasis, and inducing inflammation [43, 44]. In addition, these structures contribute to the polyamine metabolite pool altering the cancer metabolome and inducing colon cancer growth and progression [43, 45]. However, bacteria originally studied in oral biofilms were also detected in healthy individuals. It was found that a high abundance of *Lachnospiraceae* avoided the colonization of colonic tissue by oral-like bacterial networks, suggesting that certain microbiota types can protect against CRC, possibly by conferring colonization resistance. Interestingly, these protective types might be dependent of a healthy diet [39].

Some people expected a future similar to that of *Helicobacter pylori* and stomach cancer, and recently a mouse model of CRC showed that the antibiotic metronidazole partially impaired colorectal tumor growth [30]. Metronidazole is used for some genitourinary infections, but the target in that study was *Fusobacterium*

nucleatum [30]. One concern of this study, apart of the lack of a *F. nucleatum* specific antibiotic is that other players are also involved.

A novel study in humans has shown that the abundance of *F. nucleatum* in feces is strongly associated with the presence of CRC but not with the presence of advanced adenomas or non-advanced adenomas, and no association with dietary or lifestyle habits was found [46]. In other study [47], bacterial biofilms found in patients with familial adenomatous polyposis showed increased interleukin-17 and DNA damage in colonic epithelium and faster tumor onset and greater mortality when transplanted to mice. However, their predominant species are *Escherichia coli* and *Bacteroides fragilis* [47]. These observations support the hypothesis that *Fusobacterium* is a passenger that multiplies when the tumor environment is favorable rather than a causal factor in tumorigenesis. Recent reviews [48, 49] discuss this issue, concluding that both initiation and progression of CRC require the organization of these higher-order structures of bacterial communities termed biofilms [50]. Flynn et al have proposed a model in which initial changes in the normal gut microbiota allow oral bacteria such as *F. nucleatum* to colonize the gut mucosa disrupting the epithelial barrier, and to form biofilms with early and late-colonizing microbes; and the persistent state of inflammation in the colon sustaining both the biofilm and the tumorigenesis [50]. Interestingly, although biofilm formation has been explained as a cooperative enterprise of strains and species for a common goal, biofilm formation should be understood as a response to ecological competition [51].

Strikingly, the presence of *F. nucleatum* in CRC has been related to the process of metastasis, at least to the liver [30] and lymph node [38]. Although the mechanism is unknown, these bacteria might interact with the metastatic cells [30] and not only be present in the mucosal microbiota where they can adhere to epithelial tumor cells or be found inside the cells [30, 52]. Very recently it has been suggested that *F. nucleatum* orchestrates on tumor cells a molecular network of the TLR4 and MyD88 innate immune signaling as well as specific microRNAs that activate the autophagy pathway and mechanistically control CRC chemoresistance [52].

Likewise, there are another examples of biofilms associated with cancer, such as *Salmonella typhi* and development of gallbladder cancer [53], and others should be expected in the multiple organ systems spanning these microbial networks [54].

In this sense, the use of probiotics should also be tested for a hypothetical long-term effect on metastasis or recurrence in patients with these CRC-related microbiota [51, 55]. Emerging human microbiome intervention strategies have been recently reviewed [18, 56, 57]. In addition, conventional chemotherapeutic regimens might be affected by this CRC microbiota and/or will modify it.

2.2. Obesity, metabolic syndrome, cancer cachexia, stress and microbiota

Recent studies have confirmed the association between obesity and cancer susceptibility and survival after detection, including CRC [58, 59] despite the so-called “obesity-paradox” [60]. There are still many challenges exploring the association of cancer with overweight and obesity, but consensus exists about that long-term efforts in prevention should remain focused not only on further reduction of smoking but also engaging in healthy lifestyles, balanced diets and regular physical exercise [58, 61, 62].

Metabolic syndrome is a controversial concept associated with abdominal obesity, blood lipid disorders, inflammation, insulin resistance or full-blown diabetes, and increased risk of developing cardiovascular disease. Abdominal obesity is the most prevalent manifestation of metabolic syndrome and a marker of ‘dysfunctional adipose tissue’ [63] or *metaflammation* [64]. This metabolic inflammatory state is chronic and low-grade, and has been found not only in adipocytes but also in stromal and immune cells of metabolic tissues that include liver, muscle, pancreas or brain, in response to an excess of nutrients and energy [64]. Decades of research have identified the complex signaling networks between immune response and metabolism, and the cellular and molecular events that take place in situations of altered nutrient or energy flows [7, 13, 14, 15, 16, 65, 66]. Maintaining this delicate balance is crucial for health.

How risk factors in general interact with commensal flora in colorectal carcinogenesis has been reviewed [7, 10, 21]. A recent review exposes how obesity alters the microenvironment of adipose tissue affecting the adipokine secretome, with actions on remote tissues [67]. Moreover, adipocytes, like tumor cells and macrophages, also express TLR 2 and 4. These receptors in adipose tissues can be reached not only by nonbacterial agonists such as diet saturated fatty acids, but also by the commensal flora or their bacterial products such as LPS and lipopeptides, and activate them (rev in [11, 13, 21, 68, 69]).

Obesity is also associated with changes in the composition of the gut microbiota. Overall, bacterial diversity of obese individuals is reduced, in the rate between phylum (an increase in *Firmicutes* and a corresponding decrease in *Bacteroidetes*), and in the representation of genes and metabolic pathways that favor energy harvest in bacteria [70].

Intestinal microbiota imbalance (dysbiosis or dismicrobism) has been suggested as the link between IBD, CRC and Type 2 diabetes (T2D) [22, 40, 41, 42, 71]. However, the arrival of the concept of *enterotype* suggests that this knowledge will be enhanced soon [72, 73]. Although we did not find any report linking gut

Fusobacterium nucleatum with obesity, it has been recently reported a relationship of obesity with the subgingival microbiota in periodontal disease [74].

Inflammation and energy metabolism are linked in the wasting syndrome, also called cancer cachexia, present in many patients of certain types of cancer at advanced stages [75, 76, 77]. For example, liver metabolism in cachexia leads to suppression of antitumor immunity mainly through IL-6 [78]. Importantly, this axe of interactive metabolic pathways and immune system can be targeted by psychological stress, particularly those pathways mediated by the sympathetic nervous system [79]. For a general review of the tight coordination between the immune and nervous systems see the review by Talbot S et al [80].

The central nervous system also influences the commensal microbiota through several pathways of the gastrointestinal physiology, for example neurotransmitters affecting epithelial functions such as cell permeability and their production of mucus and antibacterial peptides. Conversely, gut microbiota is interacting with local and systemic inflammatory and immune cells and activating the production of inflammatory metabolites such as cytokines that may reach the brain and affect behavior [81, 82, 83]. This bidirectional axe nervous system-intestinal microbiota can also be, therefore, targeted by stress. Stress is likely to alter the innate immune responses to pathogens generating dysbiosis. Alteration of the gut *enterotypes* can modify the inflammatory environment and, with the consequent feedback loop, affect the energy metabolism, not only in the tumor but also systemically.

2.3. CRC prevention by nonsteroidal anti-inflammatory drugs

After many studies had shown that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) used in a daily basis for extended periods (at least 5 years of aspirin use) reduced the risk of CRC or polyp recurrence, and a recommendation against its use for the prevention of CRC by the U.S. Preventive Services Task Force (USPSTF) in 2007 [84] because of the considerable damage induced to stomach and intestinal lining, or even brain bleeding [85], the USPSTF reversed that position in 2015 [86,87]. Low-dose aspirin use among certain subgroups of adults distinguished aspirin as the first pharmacologic agent for chemoprevention of cancer in a population not characterized as high risk [88, 89]. Additional research into the effect of long-term aspirin use on the overall incidence of cancer according to a range of doses and by subgroups, including age, sex, baseline cancer risk, or comorbid conditions [90, 91], as well as on the additional impact of aspirin use in the setting of CRC screening, including colonoscopy already associated with a significantly lower risk of CRC [89, 92], was addressed in a 2016 study by two large prospective U.S. cohort studies [93]. Regular aspirin use could prevent many thousands of gastrointestinal tumors per year only in the USA, taking into account that only 58% of the eligible population had undergone an accepted screening option [94,

95]. Noteworthy, the regular aspirin use could also prevent CRC among the adults aged 50–75 that underwent CRC screening, as the risk of developing distant metastasis (for overall cancer) is also reduced [93, 96, 97].

Mechanistically, typical NSAIDs aspirin and ibuprofen inhibit cyclooxygenases COX-1 and COX-2. Both enzymes catalyze the production of prostaglandins from fatty acids. COX-2 is up-regulated in tumors at early stages of most cancer types [98, 99, 100, 101, 102, 103]. Inhibition of COX induces apoptosis and prevents the growth of neoplastic lesions (rev in [104]).

However, the effects of COX-2 and prostaglandins are complex because affect also the inflammatory microenvironment and not only the transformed epithelial cells (reviewed in [101, 102, 103]). Also, the tumor growth inhibitory properties of NSAIDs cannot be reversed by addition of prostaglandins, and NSAID-related metabolites that do not inhibit apparently the enzymatic activity of COXs retain their anti-tumor properties. Consequently, there are other COX-independent targets of NSAIDs; the identified so far include signaling pathways such as WNT, AMPK and MTOR (reviewed in [105]) and, in the last years, the nucleoli-dependent regulation of NF- κ B transcriptional activity that participates in apoptosis [104].

It has been also proposed that aspirin acetylates COX-1 in platelets consequently inactivating their function, and that this is the only mechanism that can explain the anti-tumor properties of aspirin when taken at low dose, but COX-1-independent effects of aspirin in platelets have also been observed (revs [106, 107]).

Efforts to overcome the limitations of side effects in the initial trials included the use of drug combinations and repurposed or chemically modified NSAIDs such as indole acetic acids, N-phenylanthranilates and aryl propionic acids, and derivatives of sulindac, nitro-NSAIDs and phospho- NSAIDs (second generation NSAIDs) that would retain the anti-inflammatory activities of traditional NSAID without blunting the gastrointestinal cytoprotection sustained by COX1-derived products such as PGE2 (reviewed in [108, 109, 110]). Overall, the clinical trials using NSAIDs for cancer prevention strongly supports the notion that inflammation is an underlying cause of cancer.

However, as minimal gastrointestinal damage and cardiovascular toxicity has not yet achieved [111], other anti-inflammatory drugs targeting different pathways, or in a different way, are being studied. Among the numerous *in vitro* and *in vivo* studies that have demonstrated phytochemicals strong antioxidant, anti-inflammatory and anti-cancer properties by regulating specific signaling pathways and molecular markers, the role of sulforaphane, curcumin and resveratrol on prevention and inhibition of CRC development should be noted in particular [112, 113]. The latter review summarizes the antiproliferative actions of resveratrol and its derivative 2,3,5,4'-tetrahydroxystilbene-2-O- β -glucoside (THSG).

2.4. Oral biofilms and periodontitis prevention by NSAIDs

Severe chronic periodontitis affects around 11% of the global adult population [114]. Periodontal disease is caused when biofilms replace the commensal microflora on the dental plaque surface and promote the chronic inflammatory destruction of periodontal tissue. In dentistry, the effects of biofilms on caries and periodontal diseases, and also in oral cancer, are well known, and approaches to fight biofilms are multiple (reviewed in [115, 116, 117, 118, 119]). A recent review have summarized current understanding of the metabolism of the oral microbiome: Saccharolytic bacteria—for example *Streptococcus*, *Actinomyces*, and *Lactobacillus* species- convert carbohydrates into organic acids, which are responsible of dental caries. Proteolytic/amino acid-degrading bacteria, including *Prevotella* and *Porphyromonas* species, by deamination finally produce short-chain fatty acids, ammonia, sulfur compounds, and indole/skatole, all of them virulent factors in periodontitis and oral malodor and that can cause oral cancer [120].

Fusobacterium nucleatum is also an important periodontal pathogen present in the bacterial complexity involved in the development of the biofilms [54, 121] and in the locally orchestrated immune responses of the gingival fibroblasts, the first line of defense against oral microorganisms [121]. Likewise, in infected oral epithelial cells, *Porphyromonas gingivalis* activates NF κ B and MAPK pathways [122] and the growth and adherence of *Staphylococcus aureus* are enhanced through the PGE2 produced by the activated COX-2/PGE2 axe [123]. *S. aureus*, as well as other strains previously thought to be non-producers of biofilms, are always associated with biofilm producer bacteria in this type of polymicrobial colonization [124]. Interestingly, aspirin and other NSAIDs are efficient inhibitors of biofilm formation [125, 126, 127, 128, 129] and may control periodontitis though the inhibition of the gingival tissue microbioma-related inflammation [74, 130, 131], as in the examples cited above [122, 123]. Resveratrol and its glycosylated derivative THSG [113] have been, intriguingly, proposed for possible complementary treatments for periodontitis through their inhibition of *Porphyromonas gingivalis*-induced inflammatory responses in human gingival fibroblasts [132].

Recent studies demonstrated a functional relationship between platelets and tumors (reviewed in [105, 106]). Consequently, chemopreventive properties of aspirin may also depend, in part, from its direct modulation of platelet biology and biochemistry [105, 106].

Intriguingly, platelets enhance biofilm formation [133], pointing to the idea that another effect of aspirin on antitumor biology might be platelet-biofilm related.

2.5. The role of platelets in biofilm formation

Platelets, the anucleated circulating blood cells that are key players in haemostasis, tissue integrity and thrombosis by limiting blood loss and promoting wound healing, store different granules -rich in a plethora of proteins, lipids and other factors-including exosomes rich in genetic material, that they selectively release upon stimulation [134].

As mentioned, emerging studies are elaborating further on platelets as active players in all steps of tumorigenesis including tumor growth and tumor cell extravasation and metastasis. In crosstalk between platelets and cancer cells, the latter trigger the platelet granule and extracellular vesicle release when they form heterotypic aggregates, changing the platelet behaviour and phenotype and RNA profiles, plus enhancing thrombopoiesis [135]. In reciprocity, through the effect of those large amounts of factors released from platelet microparticles and exosomes with anti-apoptotic plus proliferation signals and angiogenic factors, platelets reinforce tumor growth [135]. These factors additionally inhibit the immune system function that prevents tumor establishment and growth [136, 137], and induce phenotypic changes, via epithelial-mesenchymal transition, of the tumor cells, which acquire invasiveness and thus enhance their metastatic potential [134].

In addition, the heterotypic aggregates facilitate tumor cell survival in circulation, tumor cell arrest at the endothelium, and extravasation [138]. Likewise, platelets can aggregate with inflammatory cells perhaps providing an immune-evasive advantage [136].

These findings suggested that targeting the platelet may represent one of the preventive effects of low-dose aspirin, but also that this could be a novel strategy to treat cancer [134, 135, 137], together with the notion that immunotherapy might likely to benefit from the inclusion of platelet inhibitors, not only aspirin [136].

It has been recently emphasized [137] that apart of cyclooxygenase-dependent effects in platelets, recent developments of cyclooxygenase-independent effects include many protein targets of aspirin-mediated acetylation.

However, the existence of bacteria-platelet aggregates hasn't yet been contemplated in the field of oncology. But this reality is well known in other fields and should be taken into account as can be exemplified with several periodontitis-related bacteria. *S. aureus* causes, among other infections, infective endocarditis, a disease characterized by "vegetations", a structure composed of platelets, bacteria, host factors such as fibrin, and bacterial products such as the β -toxin, a virulence factor with biofilm ligase enzymatic activity that also modulates platelet function [139]. In fact, a number of *Streptococcus* species have been found to interact with platelets and form thrombus (clots) in the blood [140]. *S. gordonii*, also amongst the common

pathogens isolated from subjects with infective endocarditis, is ubiquitous within the human oral cavity. Two of their cell surface proteins mediate adherence and activation of platelets, binding to cellular fibronectin and vitronectin, and also promote formation of biofilms [141, 142]. Platelet aggregation was promoted by biofilms of oral bacteria in vitro, including *P. gingivalis* [142, 143, 144]. Interestingly, some commercially known antiseptic mouth rinses inhibited the aggregation [142]. Other biofilm-associated and platelet-binding bacteria described are *Aerococcus urinae* and *Enterococcus faecalis* [145, 146].

Another place where anaerobic bacteria/platelets aggregate is the storage devices of platelet concentrates that are used in transfusions [147, 148]. Bacterial contaminants have been implicated in adverse transfusion reactions worldwide because biofilms are a chief virulence mechanism in these hospital-acquired chronic infections [149, 150], and how to prevent the biofilm formation is being investigated [150].

2.6. Platelets and dissemination of biofilms

The formation of heterotypic aggregates is related to the two present hypotheses that try to explain how biofilms disseminate from the oral cavity to the colon, which remains to be elucidated [50]. One is a systemic dissemination from the ulcerated gingival pockets into the bloodstream that allows *P. gingivalis* or *F. nucleatum*

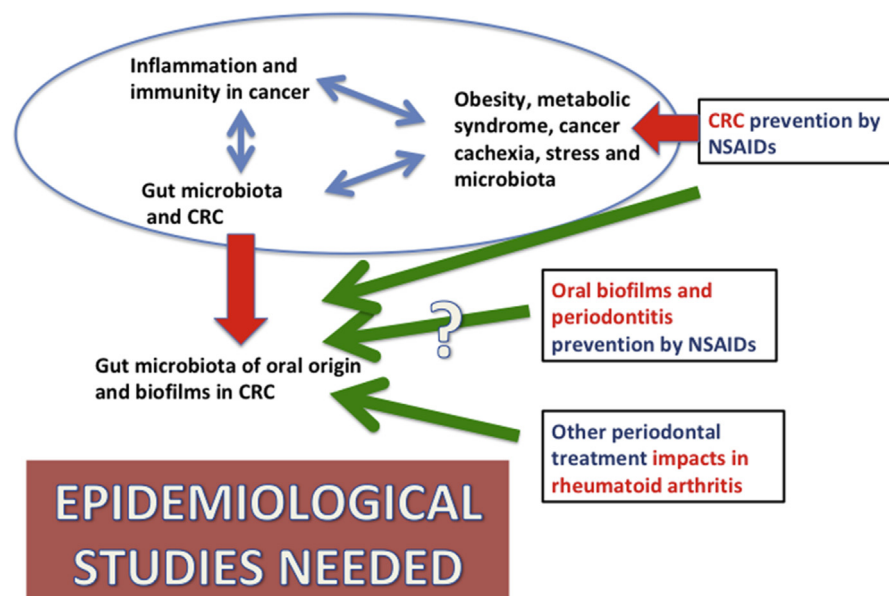


Fig. 1. The red arrows point to demonstrated events in CRC: the role of biofilms and oral microbioma in inflammation-driven tumorigenesis and the preventive role of aspirin in CRC. The green arrows hypothesize that a) one of the pathways affected by aspirin might be the formation of biofilms in the gut; b) advances in periodontitis prevention, by NSAIDs or dental plaque cleaning might impact in cancer prevention; c) the latter has shown an impact on rheumatoid arthritis. However, only two epidemiological studies so far have suggested this relationship between periodontitis prevention and cancer.

access to the colon. In this context a biofilm-platelet complex make sense [133, 139, 140, 141, 142, 143, 144, 145, 146]. These species have been implicated in other diseases such as adverse pregnancy outcomes including stillbirth, liver cirrhosis, and rheumatoid arthritis [151]. Interestingly, the role of *P. gingivalis* in the breaking of tolerance and development of autoimmunity in rheumatoid arthritis has been extensively studied [42, 114]. A similar route may be via lymphatic drainage [152].

Other alternative route of infection [151] that cannot be ruled out is via swallowing of oral bacteria that reach the colon and alter the state of the microbiota in some of the explained ways [51].

3. Conclusions

Microbiota dysbiosis plays a role in carcinogenesis at organism-external environment interfaces such as the gut and the upper gastrointestinal tract but also the oral and bronchioalveolar mucosas or skin [48, 123]. Microbiota associated to periodontal disease has been implicated in CRC carcinogenesis through different not well-understood mechanisms. These typically oral anaerobic species form biofilms, a known virulence factor.

Periodontal treatments, such as supragingival scaling or root planing, have been already shown to have an impact in rheumatoid arthritis [153, 154]. As aspirin and other NSAIDs are efficient inhibitors of biofilm formation [125, 126, 127, 128, 129, 130, 131, 132], this might be another role of the anti-tumor effects of aspirin, through inhibition of inflammation in the oral mucosa and/or avoiding gut colonization by biofilms or biofilm/platelet aggregates. Aspirin or related NSAIDs might be included in the daily tooth cleaning as well as local antibiotic therapies. However, the developments to inhibit dental plaque biofilms in humans are in pre-clinical phases.

Finally, future multidisciplinary studies ought to have in mind the inclusion of patients' data about routine professional cleaning of dental plaques in epidemiological databases (Fig. 1). To our knowledge, only two epidemiological studies of this type have suggested [155] or showed [156] this direct relationship between periodontitis and cancer. If that relationship could be confirmed, oral hygiene might be a safer and easier approach to prevent CRC and probably other cancers and diseases, as it has been already suggested [157].

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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