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Commensal microbes and p53 in cancer progression

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Abstract

Aetiogenesis of cancer has not been fully determined. Recent advances have clearly defined a role for microenvironmental factors in cancer progression and initiation; in this context, microbiome has recently emerged with a number of reported correlative and causative links implicating alterations of commensal microbes in tumorigenesis. Bacteria appear to have the potential to directly alter physiological pathways of host cells and in specific circumstances, such as the mutation of the tumour suppressive factor p53, they can also directly switch the function of a gene from oncosuppressive to oncogenic. In this minireview, we report a number of examples on how commensal microbes alter the host cell biology, affecting the oncogenic process. We then discuss more in detail how interaction with the gut microbiome can affect the function of p53 mutant in the intestinal tumorigenesis.

Keywords: Microbiota, p53, Tumour suppression, Oncogenes, Microenvironment

Background

In addition to the genetic factors [1], microenvironmental components certainly influence cancer progression and initiation, as clear evidence emerged on the contribution of integration of extrinsic and intrinsic factors in the disease pathogenesis [2, 3]. Genomic studies have clarified the genetic basis for several malignancies [4–6], as for examples neuroblastoma, which shows a clear pattern of mutations with a well-defined prognostic value [7–11]. In a wider perspective, however, distal interaction among different organs can also contribute to pathogenesis of cancer. The gut microbiota has emerged as determinants not only for the health of gastrointestinal tract (GI), but also for distal districts such as brain, pancreas and liver [12–15]. Causative links between dysbiosis and neurodegeneration, diabetic, obesity and cancer have been postulated and in part also demonstrated [16–19].

Colorectal cancer (CRC) is directly linked to gut microbiota. CRC-enriched bacteria have been identified with faecal metagenomic approaches on patients with CRC [20, 21]. These include *Parvimonas micra, Fusobacterium nucleatum, Bacteroides fragilis, Porphyromonas asaccharolytica, Thermanaerovibrio acidaminovorans, Prevotella intermedia and Alistipes finegoldii* [22, 23]. They may serve as diagnostic markers of diseases; they may also direct on a better understanding of the CRC pathogenesis and may provide therapeutic strategies in the future.

An important aspect that links dysbiosis and cancer pathogenesis is inflammation. Bacterial infection can indeed result in cancer. Gastric infection with *Helicobacter pylori* causes persistent inflammation and gastritis, resulting in a significant proportion of individuals in stomach malignancies [24]. Similarly colitis can result in tumorigenesis [25, 26, 27]. The microbiota is altered by the colitis-associated inflammation as well as altered microbiota might be causative of colitis. Interaction with host and commensal bacteria seems to have crucial implications on human health. There is indeed a fine

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balance between microbiota, inflammatory response and immune system that influences tumorigenesis.

Here, we will summarise major recent advance on the interaction between microbiota and human malignancies, with a particular focus on GI conditions. We will also discuss the potential paradoxical impact that microbiota can have on tumour suppressive mechanisms, such as the recently reported effect of switching mutant p53 from tumour-suppressive to oncogenic role [28].

The microbiota in Cancer progression

Dysbiosis is generally associated to commensal microbes outcompeted [29]; this can favour establishment of pathogenic microbes that might have causative roles in cancer (Fig. 1). Antibiotics can be the cause of outcompeting gut commensal microbiome, thus facilitating establishment of pathogenic bacteria colonies that ultimately may lead to inflammation and in specific circumstances to cancer. A deep understanding of the consequences of gut dysbiosis and the molecular basis of these represent a priority to direct research efforts in the area of cancer pathogenesis [30].

Several bacteria strains have been identified [31, 32] and associated to cancer progression and in some instance, these can produce directly or indirectly DNA damage. *Fusobacterium nucleatum* has an established role in gastric, pancreatic and colorectal cancers [33–35]. Interaction between FadA adhesin protein from *F. nucleatum* can interact with E-Cadherin, triggering activation of beta-catenin signalling, which ultimately modulates inflammatory and oncogenic responses to promote tumorigenesis. CRC patients display an elevated level of FadA protein and Wnt7b and NF*k*B2 mRNAs. Thus, FadA appears to promote tumorigenesis and *F. nucleatum* associated inflammation [36]. FadA has also been implicated in the control of natural killer (NK) cell cytotoxicity via its interaction with T cell immunoglobulin and ITIM domain (TIGIT), producing cell death in human lymphocytes [37, 38]. Also *Citrobacter* can mediate Wnt-β-catenin activation through R-spondin 2 in infected mice, producing expansion of intestinal stem cells and poor differentiation [39]. *Enterotoxigenic Bacteroides fragilis* also displays the ability to promote tumorigenesis in CRC mouse model by stimulating exaggerated immune responses via T helper 17 (Th17) cells [40]. Interaction between microbes and immune system is therefore central in the mechanisms underlying disease onset and progression.

Similarly, to *Fusobacterium nucleatum,* also *P. anaerobius* has been associated to CRC. *P. anaerobius* displays interaction ability with α2/β1 integrin expressed on colonic cancer cells by its surface protein, putative cell wall binding repeat 2 (PCWBR2). Interaction occurs on the CRC cells, but not with the normal colonic epithelial cells. α2/β1 integrin in turn activates PI3K-Akt pathway, which promotes cell proliferation, as well as inflammation via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), recruiting in the tumour microenvironment the tumour-infiltrating MDSCs and TAMs [41]. *P. anaerobius* can also interact with toll-like receptor 2 (TLR2) and TLR4 on colon cells, and modulate myeloid-derived suppressor cells (MDSCs), granulocytic tumour-associated neutrophils and tumour-associated macrophages (TAMs), thus promoting CRC [42]. In the context of this wide interplay governing the

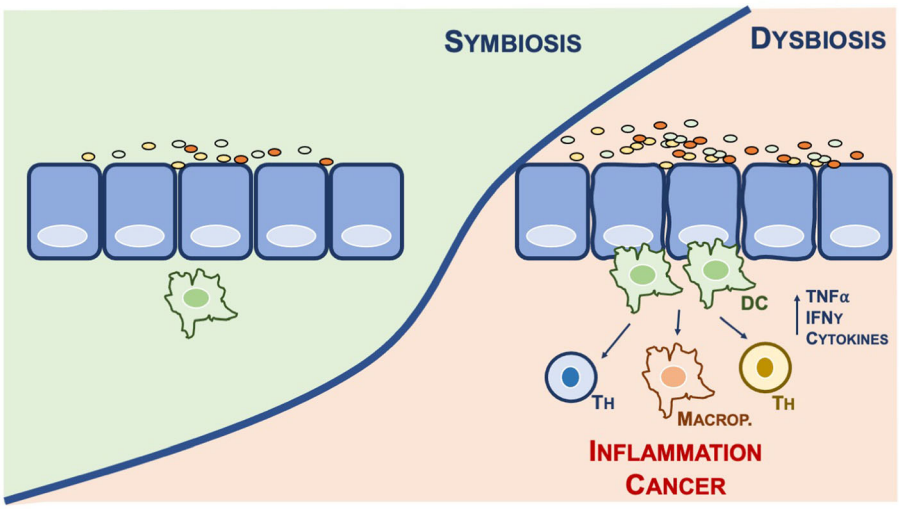

Fig. 1 Gut microbiota symbiosis vs dysbiosis. Alterations of the fine balance within commensal bacteria colonies in the gut microbiota can affect immune systems with a consequence release of pro-inflammatory cytokines and mediators, such as TNF-a and IFN-g. Recruitment of immune system can lead to sustained inflammation, which has been associated to increased susceptibility to cancer. DC, Dendritic Cells; Th, T helper cells; Marcop, Macrophages

balance between microbes, colon epithelia and immune system it becomes central the response to xenobiotics. Within these, it is of particular relevance the chemotherapy and the general responsiveness to anti-cancer therapy. Hence, efforts should be directed to examining the effect of bacterial species on chemotherapies and cancer immunotherapies and how this interplay influence the response to cancer therapy.

The microbiota in Cancer therapy

Prediction on how the gut microbiota may influence the therapeutic response to anticancer agents should take into account a myriad of intrinsic and extrinsic factors and their own interaction with each other. A large part of the altered anticancer therapy response is associated to the effect on the immune system; hence this indicates that these aspects are of significant importance for immunocheckpoint blockade therapy. However, gut microbiota has been proved to equally affect and alter response to standard anti-cancer therapy, with mechanisms that can involve or not the host immune system.

Radiotherapy represents an established curative and palliative therapeutic protocol for different types of cancers. A significant part of radiotherapy efficacy is mediated by potent immune modulatory effects, including tumour-associated antigen cross-priming with antitumor $CD8^+$ T cell elicitation and abscopal effects. Vancomycin, a gram-positive bacteria effective antibiotic, is capable of potentiating the radiotherapy-induced immune response against the tumour, thus inhibiting tumour growth in mouse transplanted B16-OVA melanoma and TC-1 lung/cervical models. Mechanistically, the effect was mediated by elicitation of cytolytic CD8+ T cells and IFN-γ response. Hence, depletion of vancomycin-sensitive bacteria is proposed to enhance the antitumor activity of radiotherapy [43].

Enterococcus hirae and *Barnesiella intestinihominis* appears involved in response to the anti-cancer immunomodulatory agent cyclophosphamide. In particular *B. intestinihominis* shows ability to promote the infiltration of IFN-γ-producing γδT cells in cancer lesions, while *E. hirae* increases the intratumoral CD8/Treg ratio by translocating from the small intestine to secondary lymphoid organs. The bioactivity of these microbes as well as the response to cyclophosphamide can be limited by the immune sensor NOD2 [44]. Memory Th1 immune cells promoted by *E. hirae* and *B. intestinihominis* showed ability to predict longer progression-free survival in patients treated with chemo-immunotherapy. *Clostridium* has been proven to be an important player in the regulation of bile acids, thus influencing chemokine CXCL16 release. Bile acids can influence production by liver sinusoidal endothelial cells of the CXCL16, which recruits natural killer T (NKT) cells to the tumour, inhibiting primary and metastatic tumour growth [45].

Effects of microbiome on chemotherapeutic response not associated to immunomodulation has also been shown. The chemotherapeutic drug gemcitabine (2′,2′-difluorodeoxycytidine), first choice for treatment of several malignancies, including pancreatic adenocarcinoma, can be metabolized by bacteria into its inactive form, 2′, 2′-difluorodeoxyuridine. Intratumor *Gammaproteobacteria* was able to promote gemcitabine resistance in a mouse model of colon cancer. Consistently a significant proportion of human PDACs (76%) were found positive to bacteria [46]. Hence, resistance to gemcitabine treatment, that currently emerges in PDAC treatment might be associated to altered microbiome [47].

p53 mutations in cancer pathogenesis

Sporadic mutations in p53 are observed more than 50% of all human cancers, while germline p53 mutations that abolish its function show a high predisposition to tumour formation in a syndrome known as Li-Fraumeni [48]. The pattern of mutations in p53 gene is very peculiar: mutations occur in the largest majority of cases as missense, leading to expression of mutant proteins. Only a small proportion (less than 10%) results in non-sense (earlier stop codon) or deletion of the gene [49].

The canonical signalling promoted by p53 results in three major biological response: growth arrest, DNA repair and eventually apoptosis [50–54]. The arrest of the cell cycle leads to a temporary arrest of the proliferation, which prevents replication of damaged DNA and the transfer to daughter cells. The p53-mediated cell cycle arrest is mediated by the transcriptional activation of p21 [55–59], which is then followed by upregulation of a large number of pro-apoptotic genes, including Puma, Noxa, Bad, Bax, Bak, p53AIP1, and Fas [57, 60–63]. The promotion of DNA repair occurs in the time-frame between cell cycle arrest and apotptosis [64–68]; if DNA repair is successful, the cell cycle resumes.

p53 neomorphic proteins [49, 69–71], associated to mutations in p53 sequence, were implicated in alteration of physiological cellular signalling, including the function of the p53 family members, p63 [72–76] and p73 [77–81] and other transcriptional factors, such as HIF-1 [82] in several different cancer types [83–85]. p63 and p73 indeed in addition to peculiar functions in epithelia [86, 87] and brain development [88–91], respectively, share with wt p53 tumour suppressive abilities, which might be altered by p53 mutants [87, 92]. These mechanisms lead to the postulation of the gain-of-function (GOF) effects of p53 mutant [69, 93–95]. Hence, mutations in p53 protein sequence appear to shift the tumour suppression function. of the wild-type protein to an oncogene form in the mutant [49, 94]. Experimental evidence has however often challenged this postulation. For example, while evidence GOF phenotypes, such as growth in vitro soft-agar assays

and in injected nude mice, have been shown for p53 R175H and R273H introduced in p53-null cells, p53 R172H and R270H genetically engineered mouse models did not show any alteration in survival when compared to p53-null mice. Consistently with the central role of functional (wt) p53 in the response to multiple cellular stressors, it might be not surprising that p53 mutant proteins also shift their behaviour when interacting with different microenvironmental conditions. Within this microbiome represents a major "extrinsic" factor that might influence p53 GOF; a recent work has indeed assessed the paradoxical effect that gut microbiome exerts on p53 mutant.

Gut microbiota: a paradoxical effect on p53 mutant

Interaction between tumour suppression mechanisms and microenvironment is crucial for the cancer cell fate. This is particularly relevant in the context of p53, a tumour suppressor that largely acts a stress response protein. A recent work has addressed the role of mutant p53 in gut tumorigenesis and in particular in the interaction with the gut microbiota. Kadosh and colleagues demonstrated that mutant p53 (R172H and R270H) exerts an evident tumour-suppressive function in the proximal mouse gut, exceeding the wild-type p53 tumour suppressive abilities. Mutant p53 was shown to substantially repress WNT-driven hyperproliferation, abrogating dysplasia in $CKIa^{\Delta gut}$ mice and tumorigenesis in $Apc^{Min/+}$ mice with a mechanism that yet is not being elucidated. Conversely however, in the distal gut p53 mutant reproduced the expected oncogenic effect. From the mechanistic perspective, gallic acid produced by gut microbiota conferred to p53 mutant pro-tumorigenic function promoting malignant phenotype. Administration of gallic acid promoted reactivation of WNT-mediated TCF4 activation and promoter binding that resulted in pro-tumorigenic effects in organoids and mouse models [28] (Fig. 2).

We recently postulated that "context is everything" for the p53 mutant GOF [96] and these recent findings seem to further sustain the importance of the context on this matter. The highly unexpected nature of the findings, however open to a number of relevant questions. These clearly include the mechanisms underlying the mutant p53 tumour suppressive function, especially in the light of the demonstrated lack of binding on the wt p53 sites, but also more general questions on the reason for a high selective pressure to accumulate p53 mutations in such a wide range of human tumours. Overall the intriguing observation, that gut microbiota has a paradoxical effect on p53 mutant switching it from tumour suppressive to oncogenic protein, highlights even more the complexity and the importance of host-microbiome interaction for the disease onset and progression.

Conclusion

Advance of the genomic technologies and computational tools in the last 20 years have significantly impacted our understanding of the genetic factors at the basis of malignancies [97–100]; more recent applications have however opened to the importance of (micro)-environmental factors on the pathogenesis of cancer. In this context microbiome has emerged as a critical player in cancer progression, not only in gut malignancies, but also more in general in distal organ-organ interactions [101]. The ability of microbiome to alter the signalling pathways of host cells is remarkable, and the recent observation of paradoxical roles in switching the function of a protein

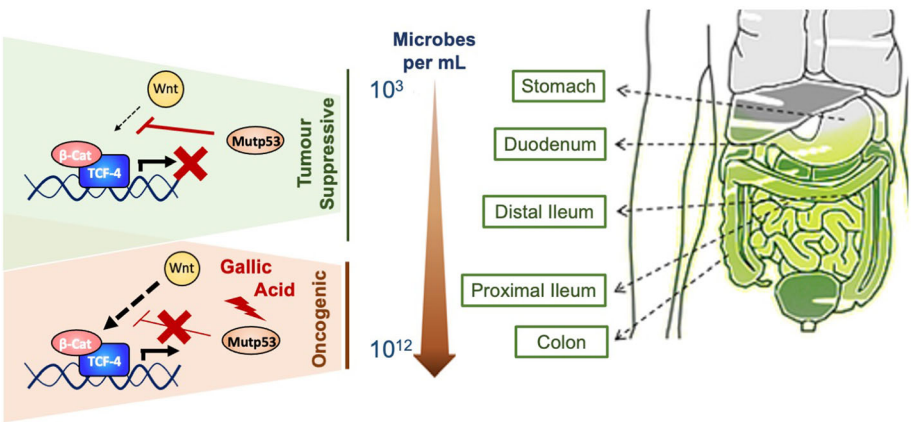

Fig. 2 Gut microbiota switches p53 mutant from tumour suppressor to oncogene. P53 mutants (R270H and R175H) have been reported to play tumour suppressive role in the upper GI tract, by inhibiting activation of Wnt/b-Cat signalling. In the distal intestine (Colon), where gut microbiota is present in higher density, bacteria-released gallic acid appears to switch p53 mutants to oncogenic activity, abrogating its capability of opposing to Wnt signalling

from tumour suppressive to oncogenic further underlies the potential of this multifactorial element in the pathogenesis of cancer. On the basis of these recent advance massive efforts should be placed in investigating the impact of commensal microbiome on the human health [102, 103]. This could be persuaded by investigating how recurrent antibiotics treatments and/or probiotics administration impact cancer incidence and prognosis to better define a significant connection between cancer and bacteria.

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IA conceived and wrote the manuscript. IC prepared the Figs. IC and GM made substantial contribution to the manuscript preparation and critically revised it. All the authors have approved this submitted version.

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Competing interests
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