An emerging understanding of the Janus face of the human microbiome: enhancement versus impairment of cancer therapy

Johan Vande Voorde, Jan Balzarini† and Sandra Liekens†

Rega Institute for Medical Research, KU Leuven, Minderbroedersstraat 10, blok x—bus 1030, B-3000 Leuven, Belgium

†Corresponding author. Tel: +32-16-337352; Fax: +32-16-337340; E-mail: jan.balzarini@rega.kuleuven.be
‡Contributed equally.

Keywords: microorganisms, anticancer agents, antimicrobial agents, chemotherapy, intestinal flora

Sir,

Commensal bacteria have been shown to modulate myeloid-derived cell functions in the tumour microenvironment that are crucial for an optimal response to immunotherapy or platinum-based chemotherapy.1 Also, the therapeutic efficacy of cyclophosphamide has been proven to be mediated by selected species of Gram-positive bacteria that stimulate a specific anticancer immune response.2 As a result, a decreased efficiency of cancer therapy was reported in germ-free or antibiotic-treated mice.1,2 These results underscore the potential risks of manipulating the microbiome prior to or during cancer treatment. Here, we want to place these findings in a broader perspective by also taking into account the, often opposite, effects microbiota might have on the anticancer activity of nucleoside-based antimetabolite drugs.

Nucleoside analogues (NAs) represent ~20% of the approved anticancer drugs and have become cornerstones of successful treatment for cancer patients.3 The clinical use of several potent NAs (e.g. flouxuridine and trifluridine) has been limited due to drug inactivation by catabolic enzymes such as nucleoside phosphorylases (NPs), which can be expressed both by mammalian cells and by commensal prokaryotes. Their therapeutic potential may therefore be improved by coadministration of a specific NP inhibitor. Indeed, TAS-102, a combination of trifluridine with the highly potent and specific thymidine phosphorylase (TP) inhibitor TPI, is currently being evaluated in a Phase III clinical trial to treat metastatic colorectal cancer.4 Non-mammalian enzymes are often characterized by a different substrate specificity or catalytic activity compared with their mammalian counterparts. Therefore, prokaryotic enzymes expressed by commensal bacteria may affect the efficiency of NA treatment or NA-related toxicity. For example, sorivudine, a potent antivaricella zoster virus agent, is catabolized (inactivated) to 5–(2-bromovinyl)uracil (BVU) by prokaryotic but not by mammalian TP upon oral administration. BVU is a potent inhibitor of dihydropyrimidine dehydrogenase, a crucial enzyme in the detoxification of the anticancer drug 5-fluorouracil (5-FU). Simultaneous treatment of cancer patients with sorivudine and fluoropyrimidines may therefore cause acute 5-FU-related toxicity and has in the past resulted in 18 fatalities.5 More recently, the cytostatic activity of several thymidine-based NAs (e.g. flouxuridine and trifluridine) was found to be compromised by ~10–150-fold in mycoplasma-infected tumour cell cultures due to the extensive expression of prokaryote-encoded pyrimidine NP (PyNP).6 Also, in contrast to mammalian purine NPs (PNPs), prokaryotic PNPs efficiently catalyse the phosphorylation of (2′-deoxy)adenosine derivatives, such as the anticancer drug cladribine. The activity of cladribine, used to treat lymphoproliferative diseases, was decreased ~10-fold in mycoplasma-infected tumour cell cultures due to prokaryote-driven drug catabolism to the inactive base 2-chloroadenine. The antitumour activity of the above-mentioned drugs could be restored by administering a mycoplasma-targeting antibiotic or a specific PyNP or PNP inhibitor.6,7 Similarly, the cytostatic and antitumour action of gemcitabine,6 used in the treatment of solid tumours, and the cytostatic activity of cytarabine,6 used for acute lymphoblastic and myeloid leukaemia, were heavily compromised due to prokaryote-encoded catabolic enzymes such as cytidine deaminase. Thus, NA-based cancer therapy may benefit from concomitant administration of specific inhibitors of prokaryotic enzymes or antibiotics to prevent drug inactivation by microorganisms.

Several studies report prokaryotic colonization of different human tumours, which may be due to aberrant vascularization of the tumour, local immune suppression, increased availability of nutrients or the presence of chemoattractants.3 When systemically administered, bacteria were shown to replicate specifically within the tumours.10 Also, a high and preferential colonization of tumour tissue by mycoplasmas compared with control or pre-malignant tissue was observed1,3 (additional references in Vande Voorde et al.1). These prokaryotes may therefore selectively inactivate NAs at the tumour site and decrease their therapeutic efficiency. However, conversely, other NAs have been shown to benefit from phosphorylation; fludarabine is selectively metabolized by prokaryotic PNP to a more toxic product5,7 (useful in combined suicide gene/chemotherapy of cancer) and capecitabine requires TP activity to exert anticancer activity.5,6
The above-described findings stress the importance of microbial metabolism (in the gastrointestinal tract or specifically at the tumour site) when treating cancer. Coadministration of antibiotics or prokaryotic enzyme inhibitors may prove beneficial for some cancer therapeutics 6–8 while for others the intact microbiota may improve therapeutic efficacy1,2,6,7 (Figure 1). Thus, the impact of the human microbiome on cancer treatment depends on the nature of the drug and argues for better understanding of drug pharmacology and for personalized medicine based on microbiome identity.

Acknowledgements
The technical assistance of Mrs Lizette van Berckelaer and Mrs Ria Van Berwaer and the editorial assistance of Mrs Christiane Callebaut are highly appreciated.

Funding
Funding was provided by the KU Leuven (GOA 10/014 and PF 10/018).

Transparency declarations
None to declare.

References

Figure 1. Schematic representation of the effect of prokaryotes on anticancer therapy. Numbers above arrows correspond to reference numbers.

Abbreviations
CpG: CpG oligonucleotides
Anti-IL-10R: inhibitory interleukin-10 receptor antibodies
NAs: nucleoside analogues
TNF-α: tumour necrosis factor-alpha
ROS: reactive oxygen species
pTH17: pathogenic T helper 17 cells
Research letters


