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Review

Induction and modulation of genotoxicity by the bacteriome in mammals

V.G. Druzhinin[a,d], L.V. Matskova[b], A. Fucic[c,*]

[a] Department of Genetics, Kemerovo State University, Kemerovo. Russia
[b] Department of Microbiology and Tumor Biology, Karolinska Institute, Stockholm. Sweden
[c] Institute for Medical Research and Occupational Health, Zagreb, Croatia
[d] Federal Research Center of Coal and Coal Chemistry of Siberian Branch of the Russian Academy of Sciences, Kemerovo, Russia

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ABSTRACT

The living environment is a multilevel physical and chemical xenobiotic complex with potentially mutagenic effects and health risks. In addition to inorganic exposures, all terrestrial and aquatic living forms interact with microbiota as selectively established communities of bacteria, viruses and fungi. Along these lines, the human organism should then be considered a "meta-organism" with complex dynamics of interaction between the environment and microbiome. Bacterial communities within the microbiome, bacteriome, by its mass, symbiotic or competitive position and composition are in a fragile balance with the host organisms and have a crucial impact on their homeostasis. Bacteriome taxonomic composition is modulated by age, sex and host genetic profile and may be changed by adverse environmental exposures and life style factors such as diet or drug intake. A changed and/or misbalanced bacteriome has genotoxic potential with significant impact on the pathogenesis of acute, chronic and neoplastic diseases in the host organism. Bacteria may produce genotoxins, express a variety of pathways in which they generate free radicals or affect DNA repair causing genome damage, cell cycle arrest and apoptosis, modulate immune response and launch carcinogenesis in the host organism. Future investigations should focus on the interplay between exposure to xenobiotics and bacteriome composition, immunomodulation caused by misbalanced bacteriome, impact of the environment on bacteriome composition in children and its lifelong effect on health risks.

1. Introduction

The multifactorial and complex mutagenic effects of living and occupational environmental settings encompass a wide range of physical and chemical xenobiotics. However, biological mutagens, including mobile genetic elements, exogenous DNA, pathogenic bacteria, viruses, are yet to be studied to a satisfactory extent.The mammalian body is inhabited by numerous bacteria and make up the most complex community, called microbiota [1]. The number of bacteria in the body is of the same order of magnitude as the number of human cells, while the number of mitochondria, derived from free-living α-proteobacteria that were engulfed by eukaryotic host cells through the process of endosymbiosis retaining 4–65 of own genes, is several folds higher than bacteria (83–677 mitochondria/cell depending on cell type) [2,3]. Therefore, the human organism should be considered as an "meta-organism" with complex dynamics of interaction between the environment, nuclear DNA, mitochondrial DNA and microbiome genome. Its number is not equally distributed in organisms, thus the highest number of bacteria has been described in the gut [2,4]. There is increasing interest regarding the investigation of the comprehensive influence of microbiota on various aspects of human health. The genetic profile of host and lifestyle factors such as diet, drugs, and environmental exposure affect the composition of the microbiota, which as feedback modulates physiological systems.

Bacteriome is initially transmitted to the infant's gut from the mother in early life. Thus, 91% of bacteria strains are shared between the mother and newborn 4 days after birth, but that figure drops to 55% one year later [5]. This shows the strong impact of the living environment on bacteriome structure.

New associations of microflora composition with various diseases have been revealed, including several forms of cancer [6–13]. Disturbances of bacterial balance caused by any factor ranging from aging to exposure to xenobiotics may launch the production of different antimicrobials or a cocktail of toxins targeting competitors [14] within the body. These compounds may be the host mutagen or re-modulator of physiological processes such as immunology response. A large number of xenoestrogens in the human environment may also have impact on microbiota same as it has been suggested that estrogen may synergize

* Corresponding author.
E-mail address: afucic@imi.hr (A. Fucic).

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with gut microbiota and have impact on obesity, diabetes and cancer [15]. Recent data showing that gut microbiota genes are capable of producing estrogen-metabolizing enzymes called estrobolom [16] is new challenge for investigations of its impact on the host estrogen/testosterone balance crucial in a number of cancer-related mechanisms [17].

Additionally, drugs disturb the delicate balance between body cells and the microbial community influencing therapy outcomes. Intestinal bacteria composition has a strong impact on the drug bioactivity and therapeutic efficacy, which opens novel therapeutic pathways that aim to restore gut eubiosis for better survival in cancer patients (Bonvalet et al., 2017). Thus for example it is shown that intestinal microflora has significant impact on the immunomodulatory effect. It is reported in preclinical investigations that improved tumor control on animal model with a combination of *Bifidobacterium* and anti-PD-L1 monoclonal antibody therapy was achieved compared to the immunotherapy alone [18]. On this basis, the authors concluded that the commensal microbiota could be regulated for clinical benefit, and postulated that the approach could be extended to other cancer immunotherapies. Similarly, pharmacokinetics of other drugs are influenced by presence of specific bacteria. Thus, increased metabolism is reported of antiarrhythmic drug (Amiodarone) in presence of Escherichia coli Nissle, Anti-parkinson drug (Levodopa) in presence of Helicobacter pylori, decreased metabolism of paracetamol in presence of Clostridium difficile etc. Proposed mechanisms are reduction in intestinal pH which facilitate enhanced ionisation of the molecule and consequently mucosal transit, upregulated expression of the influx transporter or competition in substrate such as high baseline p-Cresol levels which decrease paracetamol metabolism [19].

Recent advances in the development of molecular methods for the investigation of bacterial genomes and the use of new generation sequencing methods led to breakthrough results in the field of general and medical microbiology and metagenomics. The accumulated evidence shows that not only pathogenic, but also "normal" (symbiotic, commensal) microflora is capable of inducing mutations or modulating the mutational process in the cells of a host organism (Fig. 1).

The aim of this review is to give insight into bacterial microbiota genotoxic potency, their role in modulation of DNA damage repair, cell cycle or apoptosis in eukaryotic cells. Relevant studies were identified by systematic literature search using PubMed, Scopus and WoS regardless of the publication date.

2. Bacterial genotoxins

2.1. *Escherichia coli and Salmonella enterica serovar Typhi*

Among the large number of bacterial toxins, only three genotoxins are known to date, directly affecting the integrity of DNA in the target cells of the host organism [20]. These are the typhoid toxin (TT) produced by *Salmonella enterica serovar Typhi* [21], a cytolethal distending toxin (CDT) produced by a number of gram-negative bacteria (*Escherichia coli*, *Aggregatibacter actinomycetemcomitans*, *Haemophilus ducreyi*, *Shigella dysenteriae*, *Campylobacter jejuni*, *Helicobacter sp.*) [22] and colibactin, produced by *Escherichia coli* strains belonging to the phylogenetic group B2 [23].

Cytolethal distending toxin was detected in pathogenic strains of *E. coli* isolated from patients with diarrhea in which it caused significant cellular stretching (megacitosis) in the affected cells, hence the name of the toxin [24]. The TT and CDT are proteins with the same active subunit of CdtB, which is the functional and structural homolog of DNAase I in mammals [25]. This enzyme is capable of cleaving DNA both as a bare plasmid [26] and in highly organized form of eukaryotic DNA [27]. As CdtB's activity is about 100 times lower than that of mammalian DNAses [28] it has been suggested that this subunit may have additional enzymatic activities, for example as Mg^{2+}-dependent phosphoesters [29]. To date, it has been established that CDT binding to the membrane occurs at specific sites of the plasmatic membrane enriched with lipids, and its further transport into the cell occurs via

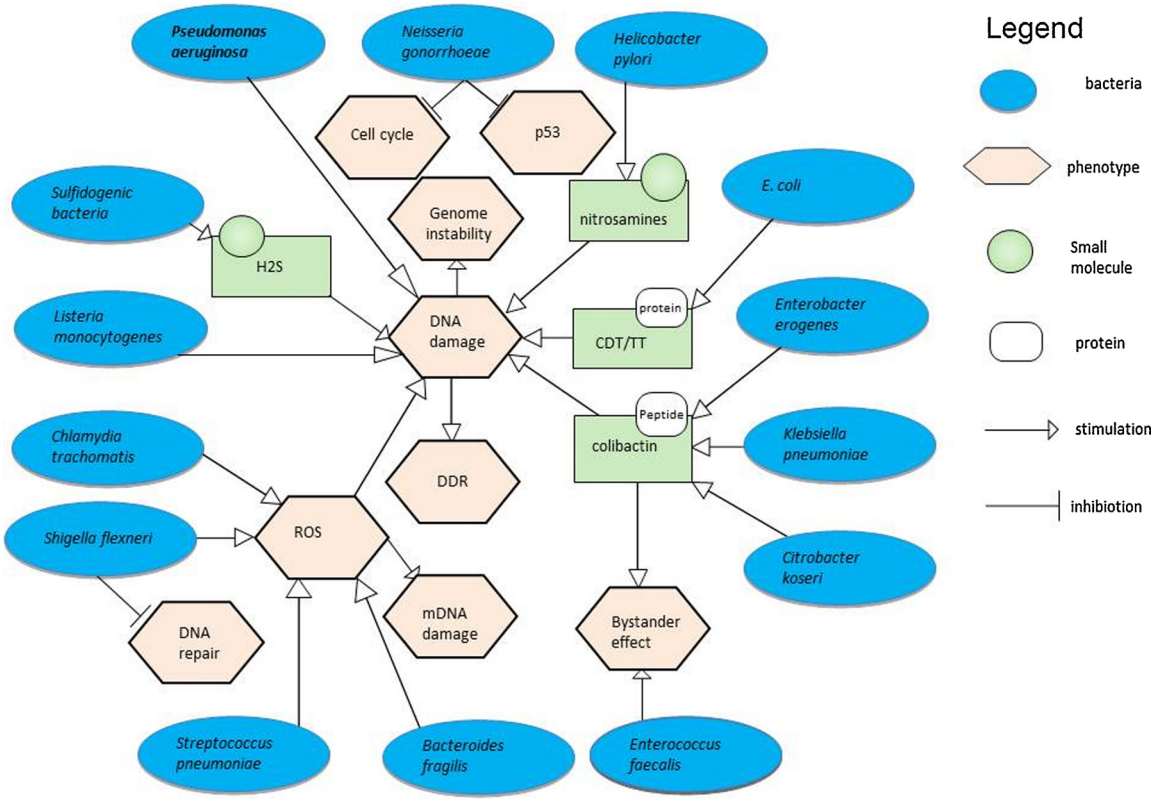

Fig. 1. Graphical presentation of different genotoxic mechanisms in host organism caused by bacteriome.