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LETTER TO THE EDITOR

The human microbiome, from Achilles armour to Nessus' shirt

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It might not be obvious but last time you used your mobile phone your ears and cheeks left the surface with a printmark of your microbiota (Meadow et al. 2014). Similarly, the printout of this article, your computer, your home and the people you share it with are subject to microbial cross-colonisation (Fierer et al. 2010; Song et al. 2013). While for decades we could rest assured that the only microbially colonised niches seemed to be our digestive system and the skin, there is now hardly any part of our bodies indeed not inhabited by microbes. This includes nasal and auditory cavities, hair follicles and sweat glands, the respiratory and the urogenital tract systems and might even include dormant remainders of infections circulating in our blood system (Bassis et al. 2015; Callewaert et al. 2014; Costello et al. 2009; Potgieter et al. 2015; Thomas-White et al. 2016). In short, apparently anything that can be reached and attached to in the human body becomes colonised by bacteria.

The implications of this microbial community that we share our body with reach far further than the occasional olfactoric reminder or the average "yuck"-factor. The microbiome project and numerous concomitant research activities start to draw a picture of a commensalic metacommunity which not only influences our digestive system and its biochemistry and physiology but also has a major impact on behaviour, immune function, reproduction, neurodevelopment, our endocrine and circadian system (Dai et al. 2015; Donia and Fischbach 2015; Leone et al. 2015; Neuman et al. 2015; O'Mahony et al. 2015; Sampson and Mazmanian 2015; Tralau et al. 2015). With a genome 100-fold the size of ours this community harbours a non-redundant gene pool of at least 3.3×10^6 genes (Qin et al. 2010; Turnbaugh et al. 2007). The metabolic and biochemical potential encoded therein far outnumbers that of the human host. First estimates put the number of possible biochemical reactions close to 1400 (including approximately 480 non-human metabolites), some of which are readily fed into our own biochemical pathways (Donia and Fischbach 2015; Ibrahim and Anishetty 2012; Jacobsen et al. 2013; Mohammed and Guda 2015). Metabolomic studies already show that in mice, for example, at least 10% of blood metabolites are directly influenced by the gastrointestinal microbiome (Wikoff et al. 2009). Given the sheer size of this commensalic cell pool and the mostly symbiotic impact on its host the microbiome is thus often considered an "organ." However, the growth dynamics and flexibility of microbial communities together with gene transfer rates 25-fold in excess of what is typically observed in soil communities equip this organ with a versatility and adaptability far beyond other organs (Smillie et al. 2011; Tralau et al. 2015). What is more, unlike eukaryotic organs the microbiome is not primarily subjected to the pressure of host well-being but strives for nutritional gain. Unsurprisingly, a lot of the microbiome's xenobiotic capability serves the primary purpose of gaining carbon, sulphur and micronutrients, respectively (i.e. Sowada et al. 2014; Tralau et al. 2015).

It is the concomitant metabolites which make microbial xenobiotic metabolism potentially hazardous and which indeed made toxicology aware of the phenomenon in the first place, when the intestinal microflora was found to interfere with the entero-hepatic cycling of contraceptives, the toxification of cycasin or the reductive degradation of L-DOPA and salicylazosulphapyridine (Aura et al. 2011;

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Meinl et al. 2009). Similarly to eukaryotic phase I and phase II metabolism prokaryotic interference with drugs can lead to substance inactivation, activation or toxicity. At least 37 established drugs are known targets of microbial metabolism as are up to 37% of drug candidates (Sousa et al. 2008; Tralau et al. 2015). However, although some prodrugs exploit canonical microbial transformations for their activation targeted screening for microbial metabolism and microbiome-mediated effects are not part of routine testing but depend on structural alerts (i.e. cleavable azo-groups) or the detection of the respective metabolites during pharmacokinetic studies or early trials. Such a case-triggered approach might be sufficient to warrant the safety of single substances but fails when challenged with more complex scenarios, be it alterations of the host's enzymatic capacities, impairment of host–microbe interactions or the effects of co-exposure. This was tragically exemplified by the deaths of several patients that occurred due to drug–drug interactions following co-exposure to 5-fluorouracil and sorivudine. Here the microbial degradation product of the latter was inhibiting detoxification of the first (Mc Connell et al. 2008; Okuda et al. 1998).

Beyond being academically embarrassing, an issue like this highlights the practical need to investigate toxicological aspects of the microbiome more systematically. This becomes also apparent by the results presented in the article of Sowada et al. (2017) where the authors report on the excretion of highly cyto- and genotoxic metabolites of benzo[*a*]pyrene (B[*a*]P) by human skin bacteria. While the toxicity of B[*a*]P as such comes at little surprise, the fact that the metabolites excreted by ubiquitous skin bacteria are not only different but appear to be more toxic than those found in eukaryotes surely does. This is the first report linking substance-induced toxicity of a widely occurring industrial contaminant to the activity of commensalic microbes. Currently, we can only speculate if and how microbial metabolites of B[*a*]P or other industrial compounds or contaminants actually do influence the host (Fig. 1). However, with the size of the chemical space humans are exposed to and the biochemical potential of the microbiome it would be foolish to assume otherwise (or to restrict the toxicology of microbial metabolites to a question of drug safety, for that matter). Systematic comparison of lists of metabolites known to be toxicologically relevant with environmental databases such as the one for biocatalysis and biodegradation at the University of Minnesota will likely reveal that there are more similarities and overlaps than just B[*a*]P (Gao et al. 2010).

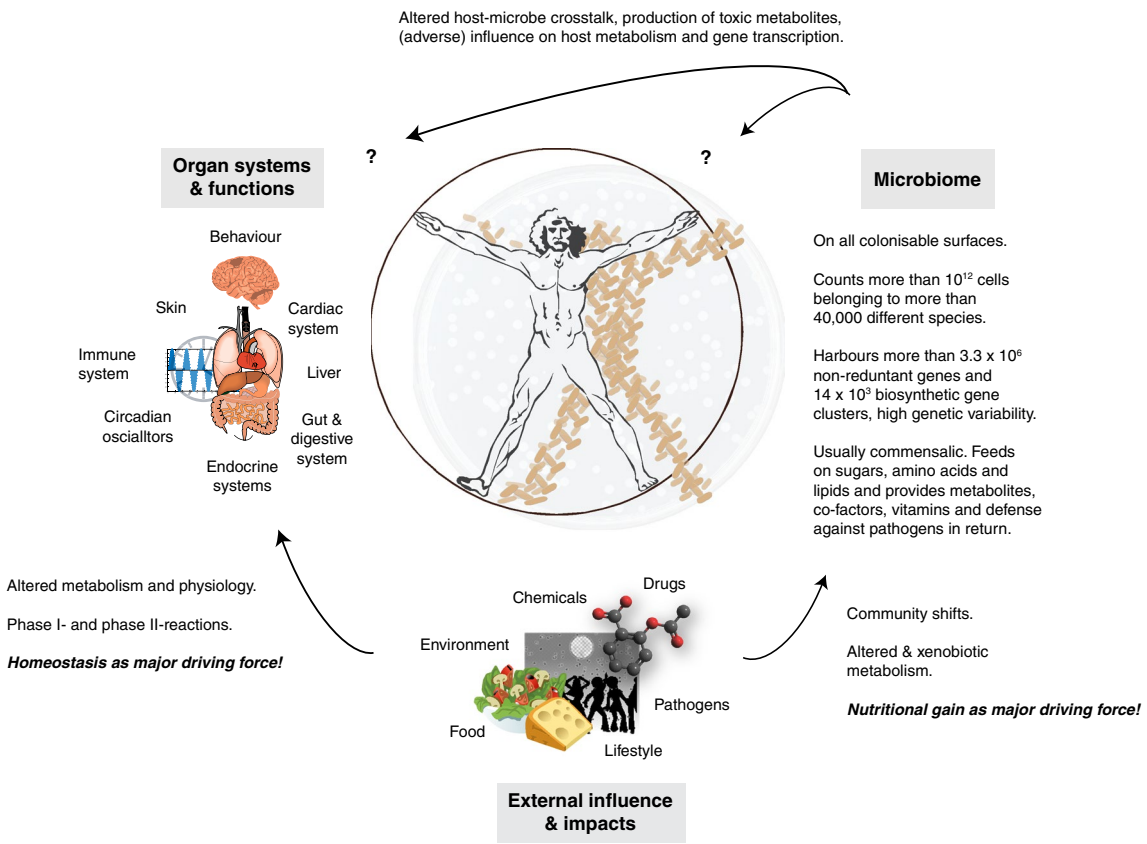

Fig. 1 Sketch depicting the role of the microbiome as "organ" and the potentially (adverse) impact of external influences

Genomics and transcriptomics allow access to microbial communities and their transcriptomic profiles, while high-resolution mass spectrometry and metabolomics can provide insight into the underlying biochemistry and metabolic processes. At the same time a variety of model systems and culturing techniques are available for the analysis of selected communities or isolated members, and soon probably also co-culture systems (Donia and Fischbach 2015; Spanogiannopoulos et al. 2016; Tralau et al. 2015). Challenging as it still might be analysis of microbiome's toxicology has thus become feasible.

The often symbiotic relationship with our prokaryotic commensals has traditionally shaped the view of an Achilles armour, be it for the provision with vitamins, protection from pathogens or immune modulation. However, it appears that there is a potentially dark side to this armour which reaches beyond the established microbial pathophysiologies. Investigating it is not only bound to provide us with an exciting new perspective on human health and toxicology but will also help to avoid it becoming a Nessus' shirt.

"We know what we are, but know not what we may be." (Shakespeare, Hamlet).

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