3.2. Is biodiversity important for health? What role does the diversity of pathogens play? (contd.)

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Microbiota and health: biodiversity at work. The intestinal microbiota, a term also used for the resident or commensal flora of the intestinal lumen (commensa = eat at the same table), is a biodiversity model: 10^{14} microorganisms, or 10 times the number of somatic and germ cells of which we are made up, a gene pool 100 times greater than the human genome, approximately 1,000 species, the same metabolic activity as the liver. The vast majority of intestinal bacteria belong to the Firmicutes, especially clusters XIVa and IV grouping together Gram-positive extremely sensitive to oxygen (EOS) anaerobic bacteria that are mostly uncultivable, and to the Bacteroidetes which comprise Gram-negative anaerobic bacteria. There are negligible quantities of other families (Proteobacteria such as enterobacteria, Lactobacillaceae, Mollicutes), which does not mean they are useless. It is tempting to consider the human microbiota to be more than just a symbiotic complex inherited from the long coevolution of both invertebrates and vertebrates, but a real additional organ which other florae join: oral, genital, skin. This leads to the notion of superorganisms tending to make a consistent whole of Man and its florae. This vision is all the more tempting as the intestinal microbiota, once formed in the first few months of life, demonstrates an extraordinary stability and a remarkable resilience, particularly following antibiotic treatment in which an almost full recovery of the constituent species and their main balances is seen. A sort of healing. From this point of view, the human genome and the genome of its microbiota can be considered as a whole, now known as a hologenome.

Without the microbiota, many plant and animal species, humans for one, would not have appeared or would have disappeared, with entire phyla becoming extinct in critical periods when the ecological and climatic conditions made the presence of commensal bacteria vital. Under this selective pressure, the microbiota has established itself, with the intestinal bacteria performing major metabolic functions such as the hydrolysis of complex plant polyosides that large primates are unable to digest. What about cooling periods when our ancestors had only leaves and roots to eat? Bacterial biodiversity saving the biodiversity of vertebrate species? Poetic justice for anyone who only sees the microbial world as the smallest minority of pathogens. The intestinal microbiota also performs many other vital functions such as biosynthesis of vitamins and detoxification of toxic substances in the diet (xenobiotics). It also acts as an extremely effective barrier to non-indigenous microorganisms, especially pathogens which have to, in order to effectively colonise their host, oust and destroy this commensal flora “barrier”. Actively pursued metagenomic studies (comprehensive analysis of the genomes of a complex flora) will provide an unimaginable number of coding genes for the effectors of these complex functions. Diving into the biodiversity of our commensal flora promises spectacular developments in fields as varied as animal and plant biology, medicine, biotechnology, etc.

But it comes at a price. Maintaining this microbiota has posed problems for all species and the scars of this adaptation are starting to be identified, amongst invertebrates such as the fruit fly, or amongst mammals. The immune system, in particular the innate immune system, had to form when performing the difficult task of controlling such a diverse microbiota to prevent the host being overwhelmed by it, while taking care not to eradicate it. This coevolution has revealed a network of complex sensors, signals and effectors leading to an “armed vigil” situation. Whether it is characterised as tolerance or physiological inflammation, it illustrates the traditional *si vis pacem, para bellum* principle and has also formed a true symbiosis as the presence of the microbiota is essential for the postnatal maturation of the immune system, in particular the mucosal immune system. To these constraints is added the need for the immune system to distinguish occasional pathogenic bacteria from permanent commensal bacteria and to respond in a suitable way to the threat when it arises. Recognising a restricted biodiversity, that of pathogenic bacteria, within a broader biodiversity, that of the commensal and/or symbiotic microbiota, is undoubtedly the second constraint which has formed the main balances in the immune system.

Here we get to the heart of the matter regarding the biologically diverse interface of the world of microbes and that of animals, particularly humans. The essence of the discrimination between commensal bacteria and pathogenic bacteria lies less in the nature of the bacterial motifs (lipopolysaccharides-LPS-, lipopeptides, flagellin, muropeptides) recognised by the innate immunity receptors (Toll-like receptors, Nod-like receptors, scavenging receptors) than in the perception of a danger, a second signal superimposing itself upon recognition of prokaryote motifs. This danger signal corresponds to the host’s response to the expression by the pathogenic bacterium of effectors such as adhesins, invasins, membranolytic toxins, secretion equipment for injecting effectors into the cells, intracellular growth, etc. These effectors lead to very efficient proinflammatory signals mediated by pathways such as the NF-kB pathway and the MAP Kinases cascade, and by the inflammasome. In themselves they represent the markers of a biodiversity generated under the selective pressure of the host’s responses via the accumulation of genes or gene combinations (pathogenicity islands) comprehensively providing a “turnkey” pathogenic property, i.e. an ability to colonise a surface, invade it, cause its inflammatory destruction and finally effectively infect the host despite its defence mechanisms.

Above a certain limit perceived as characteristic of the danger, the host will respond but what about the subthreshold situation? Are the commensal bacteria making up the microbiota also unable to stimulate a danger signal despite their taxonomic diversity, or do they represent a complex community of individuals, some stimulating immune response almost up to, or even above, the danger threshold, others actively inhibiting these responses? Are we, after a fashion, in the presence of a single null vector or several vectors, some positive and others negative, the result of which is below the danger threshold? Recent data seems to support the second theory. SFB (segmented filamentous bacteria), a commensal clostridial species anchored in the apex of the intestinal epithelium, provoke a mucosal inflammatory type of response (Th1, Th17), while a Bacteroidetes, *Bacteroides fragilis,* produces a highly anti-inflammatory capsule. It is probably through careful selection within microbial diversity that our commensal florae are created. There is clearly an optimum combination responding to metabolic and immunological needs. Forthcoming

analyses – handicapped however by the persistent problem of cultivating many of these bacterial species – will give meaning to this controlled diversity.

New pathology fields, linked to poor microbiota management, can already be seen burgeoning in medicine, according to the careful analysis of molecular and cellular infections by pathogenic bacteria. Obesity, insulin resistance, linked to a microbial imbalance or dysbiosis, favouring bacterial species more suited to metabolising the alimentary bolus and storing energy. Inflammatory diseases of the intestine linked to poor management of the signalling network leading to the tolerance of the microbiota, the most aggressive members of the commensal bacteria, the “pathobionts”, gaining the upper hand and maintaining a danger level above the critical threshold.

By way of a conclusion, let us try and look at the biodiversity of our microbiota in terms of a society. Every society has its delinquents (pathogens, pathobionts) that need to increase the level of combat (anti-inflammatory microorganisms) but that also reveal weaknesses and imbalances in this society (dysbiosis). It also has its altruists, its egoists, its workers, its idlers, but above all its inert members which form the largest contingents but which undoubtedly ensure the resilience of the system. Let us suppose that a significant part of the pathology turns out to be linked to imbalances in the biodiversity of the microbes that colonise us. It is a new paradigm that represents a change of scale in microbiology and will call for an adaptation of minds and technological resources, in particular diagnostic tools.