Natural immunity

Biodiversity loss and inflammatory diseases are two global megatrends that might be related

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We are witnessing two global and deeply worrying trends that, at first glance, seem unrelated. The first trend is the ongoing decline in biodiversity, which is caused by human actions. It could well become the sixth mass extinction of animal and plant species on Earth, comparable in magnitude with the fifth mass extinction at the end of the Cretaceous, 65 million years ago. The second trend is a rapid increase in chronic diseases that are associated with inflammation, especially in developed countries (Fig 1). Inflammation is a key attribute in asthma and allergic diseases, autoimmune diseases and many cancers; even depression has been associated with the presence of inflammatory markers. In this article, we argue that these two phenomena are more closely related than commonly thought: declining biodiversity might actually increase the risk to humanity from chronic diseases and thereby cause a major public health problem.

We thereby extend the hygiene and microbial deprivation hypotheses to a biodiversity hypothesis, with inevitable consequences for public health

The underappreciated link between biodiversity and human health are microbes, which inhabit all ecosystems, including the human body. Although microbial life on Earth as such is not threatened—unlike many plant and animal species—the diversity and abundance of microorganisms in affluent urban environments has clearly declined (Alenius *et al*, 2008), which raises intriguing questions. What are the effects of the loss of biodiversity of plants, animals and their habitats on the environmental

microbiota? What is the relationship of the microbiota living on our skin, in our respiratory system and in our gut, with the environmental microbiota? What are the effects of any changes in human bacterial communities on human health?

Our proposal would expand the ‘hygiene hypothesis’, which posits that environments rich in microbial diversity confer protection against allergic and autoimmune diseases (Rook, 2009). While the hygiene hypothesis mainly focuses on microbes in the home, in food and drinking water and on domestic animals, we believe that it should include our living environment in general. We thereby extend the hygiene and microbial deprivation hypotheses to a biodiversity hypothesis, with inevitable consequences for public health.

Biodiversity means, by definition, “the variability among living organisms from all sources, including, *inter alia*, terrestrial, marine and other aquatic ecosystems and the ecological complexes of which they are part; this includes diversity within species, between species and of ecosystems” (www.biodiv.org/convention/). In practice, the most pertinent elements of biodiversity are genetically diverse populations of many species, including cultivated plants and domesticated animals; the size and the state of natural habitats; and the functioning of ecosystems. Although the Convention of Biological Diversity is primarily concerned with plants and animals, biodiversity includes microorganisms, which are less visible but which comprise the bulk of living matter on Earth.

The United Nations’ International Year of Biodiversity in 2010 was supposed to be the turning point for biodiversity loss. Yet, a recent report confirms that the rate of

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decline shows no signs of slowing down; the various pressures on biodiversity continue to increase (Butchart *et al*, 2010). On the basis of figures from the Millennium Ecosystem Assessment, the pre-human background rate of species extinction, calculated from the fossil record, is between 0.001% and 0.01% of species per 100 years. The current rate is approximately 1% and is increasing; future projections estimate that 20–30% of species will become extinct within the next 100 years. This figure might seem high, but it is consistent with the most recent data about threatened species (www.iucnredlist.org/). Overall, one-third of the 56,000 animal and plant species that are sufficiently well known to allow the evaluation of their status are threatened. The main cause for this dramatic loss of biodiversity is major changes in land use, mostly driven by the expansion of the human population and the ensuing destruction of natural habitats.

The loss of natural habitats, ecosystems and biodiversity has drastic consequences for human health. An expanding body of evidence demonstrates how natural environments are vitally important to physical and mental health. For instance, a recent study reported an inverse association between physician-diagnosed health and the proportion of green space in the patients’ environment (Maas *et al*, 2009). Nature, and forests in particular, have substantial potential to improve human health; the International Union of Forest Research Organizations (IUFRO) has launched a task

Fig 1 | Two global megatrends in biodiversity and public health. (A) Declining biodiversity since 1970 as measured by three indices. LPI, Living Planet Index; WBI, World Bird Index; WPSI, Waterbird Population Status Index (Butchart *et al*, 2010). (B) Increasing trends in the prevalence of inflammatory diseases. Asthma and allergic rhinitis among military conscripts from 1966 to 2003 (Latvala *et al*, 2005) are shown as an example.

Table 1 | Reduced diversity and/or altered composition of microorganisms in the gut and respiratory tract is associated with chronic inflammatory diseases

Disease	Evidence from	Reference
<i>Gut</i>		
Asthma/allergy	Humans	Sjögren <i>et al</i> , 2009
Type 1 diabetes	Mice	Wen <i>et al</i> , 2008
Inflammatory bowel disease	Humans, mice	Round & Mazmanian, 2009
Obesity	Humans, mice	Turnbaugh <i>et al</i> , 2009
Behavioural changes	Mice	Bienenstock & Collins, 2010
<i>Respiratory tract</i>		
Asthma, chronic obstructive pulmonary disease	Humans	Hilty <i>et al</i> , 2010

force on Forests and Human Health to investigate further this concept (www.iufro.org/science/task-forces/forests-trees-humans/; www.forhealth.fi). Such associations between nature and health are well recognized, but we need more data and better understanding of the relevant mechanisms at the cellular and molecular levels.

The processes that link human health and environmental changes are multifaceted, complex and difficult to examine experimentally, but it is clear that microorganisms have a key role. Commensals inhabiting our skin and mucosae are not passive bystanders or transient passengers, but active participants in the development and maintenance of barrier function and immunological tolerance in humans, and it is becoming increasingly clear that human health depends on both commensal and environmental microorganisms. This microbial zoo includes bacteria, fungi, viruses and

microscopic protozoans, although hardly any data are available on the roles of the latter.

The bacteria population in the human gut has a high diversity at the genus and species level, but the community is dominated by two phyla, Firmicutes and Bacteroidetes, and to a lesser extent by Acinobacteria and Proteobacteria (Turnbaugh *et al*, 2009). Recent metagenomic data indicate that each human harbours at least 160 bacterial species, which are partly shared with other individuals. The total number of bacterial species identified in a sample of 124 Europeans was 1,000–1,150 (Qin *et al*, 2010), suggesting a

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rather distinct individual composition of the flora.

It is well known that reduced diversity and composition changes of the gut microbial community are associated with allergic disease (Sjögren *et al*, 2009); recent studies indicate similar associations with other inflammatory conditions (Table 1). The evidence from mice and humans indicates that some common members of the normal microbiota have a special role in maintaining homeostasis and health (reviewed by Round & Mazmanian, 2009; Fig 2). Changes in the indigenous microbiota might therefore readily translate into disease.

Similarly to the gut microbiota, bacterial communities on our skin are a complex ecosystem with various lines of cells that can communicate with each other and with host cells. Its members come from the same four phyla as in the gut, although with different relative abundances, as Gram-positive Actinobacteria and Firmicutes dominate (70–80%). Each body site harbours a characteristic microbiota with relatively low temporal variation (Grice *et al*, 2009; Costello *et al*, 2009). Metagenomic studies have revealed that the diversity of bacterial communities on the skin is comparable with the gut microbiota (Qin *et al*, 2010; Fierer *et al*, 2008), implying that the skin microbiota also has an important role in the immune system. The skin community, like the gut community, includes both transient and permanent members (Grice *et al*, 2009), suggesting that at least a part of the community is in dynamic interaction with the environment. Most research has been carried out and published on the gut flora and its role in health and disease, but ongoing metagenomic projects might well reveal a significant role for these other microbiota.

The role of microorganisms is fundamental for immunological tolerance and tissue integrity. Although the cause and effect are not entirely clear, literature on the development of epithelial cell tolerance and homeostasis (von Hertzen *et al*, 2011) and experiments that involve the transfer of gut microbiota (Turnbaugh *et al*, 2006; Wen *et al*, 2008) show that altered environmental microbiota and reduced Toll-like receptor signalling cause immune dysfunction, which enhances the colonization and growth of a different microbiota. This creates a self-perpetuating cycle that pushes the host–microbe system towards an ‘unhealthy’ state.

The protective mechanisms against inflammatory diseases crucially involve activation of innate and regulatory networks by continuous exposure to microbes through the skin, gut and respiratory tract; in fact, humans have evolved over millennia to coexist with microorganisms that do not elicit immune responses, but rather induce immunoregulatory circuits. Thus, reduced diversity and exposure to these microorganisms might now lead to failure to terminate and restore inappropriate inflammatory responses (Rook, 2009). Two major discoveries in immunology—the regulatory network and the Toll-like receptor system—have fundamentally improved our understanding of the role of commensal and saprophytic microbes in health and disease. The interaction of microbes with their specific receptors on and in immune cells is necessary for the development and maintenance of epithelial cell integrity, tolerance and tissue repair. In the absence of these microbial stimuli, the immunoregulatory circuits, including regulatory cytokines interleukin-10 and transforming growth factor- β , regulatory dendritic cells and regulatory T (T_{REG}) cells, are no longer adequately induced. An inflammatory milieu, in turn, might enhance the conversion of T_{REG} cells to inflammatory $T_{\text{H}}17$ cells (von Hertzen *et al*, 2011) and enrich bacteria that tolerate inflammatory mediators in the microbiota, thereby creating a self-perpetuating system (Fig 3). These molecular findings further support the hygiene hypothesis, which states that a sedentary lifestyle in affluent urban environments does not provide adequate microbial exposure for the development of a ‘healthy’ microbiota.

Epigenetic mechanisms have also received much attention during the past few years as a possible explanation of how environmental exposure modulates the immune system. Environmental factors evidently have key roles in activating or silencing genes by altering DNA and histone methylation, histone acetylation and chromatin structure, which might mod-

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Fig 2 | Epithelial cells in the respiratory tract, skin and gut are constantly exposed to both environmental and indigenous microorganisms. In addition to active transport of antigens by specialized gut epithelial cells (M cells) and their constant sampling by dendritic cells (DCs), epithelial cells recognize bacterial antigens directly through Toll-like receptors. Similarly to mucosal epithelial cells, skin epidermal cells, keratinocytes and Langerhans cells, also express a broad range of Toll-like receptors. In steady-state conditions, T_{REG} cells, through continuous stimulation of epithelial and innate immune cells, prevent inappropriate inflammatory responses by IL-10/TGF- β production. Microorganisms might also be involved in the epigenetic modulation of immune responses. FOXP3, forkhead box P3; IL, interleukin; IFN- γ , interferon- γ ; TGF- β , transforming growth factor- β ; TNF- α , tumour necrosis factor- α .

ify disease susceptibility in individuals. Vuillermin *et al* (2009) suggest that microbial exposure is linked with demethylation (activation) of the interferon (*IFN*)- γ gene in naive T cells; thus, microbial deprivation in early life is associated with persistent methylation (silencing) of the *IFN*- γ gene, resulting in reduced IFN- γ production and increased risk for allergic diseases. In general, microbe-rich environments induce both proinflammatory and regulatory circuits early in life (Schaub *et al*, 2009), indicating an early activation of the relevant genes. These observations call for more research on the role of microbial stimuli

in the epigenetic modulation of T cells, particularly T_{REG} -cell function.

Although early life is important for epigenetic modulation, significant changes might occur later, as Fraga *et al* (2005) showed in a comprehensive study of monozygotic twins. While the twins appeared to be epigenetically indistinguishable in early life, older monozygotic twins who had different lifestyles and had spent less of their lives together had substantial differences in the overall content and genomic distribution of methylation and histone acetylation—which probably contribute to discordance in disease susceptibility.

Fig 3 | In the absence of sufficient microbial stimuli, immunoregulatory circuits are not induced adequately resulting in low levels of interleukin (IL)-10/transforming growth factor (TGF)- β . An inflammatory milieu, in turn, enhances the conversion of T_{REG} cells to $T_{\text{H}}17$ cells and favours the enrichment of bacteria in the gut (and other microbiota) that tolerate inflammatory mediators, creating a self-perpetuating system. Ambient air pollution might act in synergy and further strengthen immune dysregulation by inactivating FOXP3 $^{+}$ T_{REG} cells by epigenetic mechanisms. Together, these factors probably contribute to the increase in inflammatory diseases in developed countries.

Perhaps the strongest evidence for the idea that lifestyle and environmental factors modulate immune regulation comes from epidemiological studies on immigrants. Individuals who move from areas with a low prevalence of chronic diseases to an area with a high prevalence often have a good health status after arrival: the ‘healthy immigrant effect’. However, their health eventually declines to the same level as the native population or worse. These changes seem to occur within 10 years after arrival, but are often most dramatic in recently arrived individuals (Newbold, 2005); this phenomenon is not restricted to young people but occurs also in adults (Kalyoncu & Stålenheim, 1992). This immunomodulation by cultural adaptation—which goes together with changes in disease susceptibility—seems to be a universal phenomenon for various inflammatory diseases, including asthma and allergies (Grüber *et al*, 2002; Kalyoncu & Stålenheim, 1992), autoimmune diseases (Bodansky *et al*, 1992), obesity and type 2 diabetes (Creatore *et al*, 2010), depression (Casimir *et al*, 2010) and cancer (Pinheiro *et al*, 2009). The disease spectrum is similar to that associated with altered gut microbiota, as discussed above.

The loss of biodiversity and disappearance of natural habitats pose a serious threat

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to humankind because they impair many essential ecosystem services—one of which is the role of environmental microbiota in enhancing human health. Living in dense urban environments might therefore lead to an ‘immune adaptation syndrome’—that is, the inability of the immune system to adapt to microbe-poor environments—in a large part of the population. At the population level, changes in disease prevalence are slow to become apparent—the allergy problem, for instance, became visible in the mid-1800s even when people had been living in cities for a long time. At the individual level, immune disorders often start early in life, last for a long time, might cause disability and require continuous medical treatment, which creates a considerable burden for both patients and society.

People in affluent societies have both adapted their urban environment and have themselves adapted to it in order to balance their immune system. The creation of large parks and green belts in cities or local

recreation areas certainly improve the mental and physical well-being of city dwellers. It is, however, increasingly difficult to create ‘immune-friendly’ green areas in the rapidly growing megacities. As the global population continues to grow, resources become increasingly scarce, and there is simply less vacant space. Within the next 30 years, two-thirds of the population in developing countries and almost 85% of the population in developed countries will live in urban areas with little green space (World Urbanization Prospects: The 2007 Revision Population Database; <http://esa.un.org/unup/>). Urbanization and densification continue despite the accumulating data showing that natural environments are associated with better physical and mental health.

The hypothesis that we propose—biodiversity loss leads to immune dysfunction and disease—has numerous societal and public health implications that are increasingly apparent in the developed world and will have a major impact on developing countries in the near future. Two independent lines of research—metagenomic studies of the microbiota in the gut and other sites, and immigrant studies—support our idea that inflammatory diseases characteristic of urban life in affluent countries are associated with changes in the environmental and commensal microbiota. We have already lost a huge amount of natural environments in the industrialized and developed countries and thereby depleted their biodiversity; if biodiversity loss continues unabated, the prospects for public health might indeed be bleak. The growing burden of inflammatory diseases might also enter a vicious cycle if the response is to reduce further our exposure to natural environments. Biodiversity loss works in the same direction, as it diminishes opportunities for outdoor activities and therefore encourages a sedentary lifestyle.

Chronic inflammatory disorders can be added to the long list of reasons of why we should care for the diversity of animal, plant and microbial life on Earth. We need to consider measures that not only preserve the natural environment but also reconnect us with nature. We need to preserve our connection to the soil and green spaces, we

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need to expose our children to natural environments, and we need to change food production and transportation, to mention just a few measures. Above all, however, we need to urgently stop the ongoing species extinction—as humans cause it, they also have the power to stop it. Even if molecular biology and biomedical research might eventually develop immune-stimulating treatments to address the burden of chronic inflammatory disease, these will be only paltry substitutes of nature.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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