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Antibiotic resistance- adapted immunointerventions considering microbiome

Ivana Haluskova Balter

French Society of Immunology, France

Bacteria, viruses, parasites and fungi that are resistant to drug cause 700,000 death each year. By 2050 superbugs inured to treatments could cause up to 10 million deaths annually and costs the global economy US\$100 trillion. AMR (antimicrobial) resistance is regarded nowadays as a major threat to global public health. The issue is receiving high-level political attention (G7 and G20 in 2017 for first time). The list was drawn up in a bid to guide and promote research and development (R&D) of new antibiotics, as part of WHO's efforts for AMR (27th Feb 2017). Resistance to antibiotics may arise in a population of susceptible bacteria by the accumulation of mutations (e.g. point mutations in DNA gyrase conferring resistance to quinolones) or by the acquisition of resistance genes that protect the cell against antibiotics. Antibiotic resistance genes can cause phenotypic resistance through a variety of mechanisms, including the enzymatic inactivation of the antibiotic, the modification of the antibiotic target and the prevention of the accumulation of lethal intracellular concentrations of the antibiotic through efflux pumps. Problem of resistance get worsened due declining number of new antibiotics and limited number of new classes direct research to look for alternatives. Additionally, antibiotics shape the ecology of the gut microbiota in profound ways, causing lasting changes to developing and mature microbiotas. The application of next-generation sequencing has enabled detailed views of the side effects these drugs have on commensal populations during treatment of infections. The human gut thus harbours a complex microbial ecosystem, which consists of hundreds of species, collectively termed the gut microbiota. The gut microbiota is relatively stable in healthy adults but the composition of the gut microbiota can change rapidly owing to dietary changes, illness and the use of antibiotics. Importantly, there is and evidence of existing communication between the central and the enteric nervous system, linking emotional and cognitive centers of the brain with peripheral intestinal functions. This interaction between microbiota appears to be bidirectional, namely through signaling from gut-microbiota to brain and from brain to gut-microbiota by means of neural, endocrine, immune, and humoral links. Negative impact on composition and functionality microbiota

given existing immune crosstalk including "innate cell immunity training" impact host immune response capacities observed in recent research. Imbalances in the gut microbiota can induce inflammation that is associated also with the pathogenesis of obesity, type 2 diabetes mellitus, and Alzheimer's disease. Therefore in addition to the increased threat of resistance to antibiotics caused by inappropriate use of antibiotics and important side effects on microbiota, it is clear that overuse of broad-spectrum antibiotics must be quickly phased out in favour of more precise approaches and must be complemented by efficient methods to restore the microbiota after injury. Recent advances in the development of narrow-spectrum antivirulence compounds, coupled with a renewed interest in the use of probiotics, FMTs (fecal microbiota transplantation) and phage therapy along with thoughtful development of vaccines and monoclonal antibodies represents paths in multiple approach to tackle AMR considering preservation of microbiota. FMT working principle is to restore the microbiological environment in host intestine similarly as probiotic while administrating live microorganism to confer a health benefit on the host. For both there is a need for standardised clinical protocols to help translation in clinical wider use. Moreover microbiome therapeutics are seen as potential intervention to reduce carriage of resistant pathogens. High potential of vaccines to tackle antibiotic resistance respecting role of gut microbiota as host superorganism gain evidence. One should note that vaccines like diphtheria and tetanus did not prompt resistance. In 1980 the smallpox vaccine had eradicated the naturally circulating virus worldwide without generating resistance. Additionally, introduction of live vaccines like measles and BCG has been associated with much larger reduction of mortality than can be explained by the prevention of the targeted infections and recent research around LATV highlights importance of "off target" effects to be evaluated in depth. In conclusion, alternative directions considering strongly their role on host microbiota and immune system modulation should be strongly promoted while tackling issue of antibiotic resistance.

ivankahaluskova@gmail.com