Connect to previous writing: Use of DNA to assess microbial communities

In the past, isolation prevented epidemics.

Hygiene Hypothesis

Now, modernization improved contagion.

Disappearance of microbes due to sanitation.

Importance of Microbiome in general for health

Ie Microbes improve nutrition by increasing digestable volume of food.

Bacteria metabolisms are essential.

Bacteria are predators, not evil!

Colonization is harmless.

Correlation != Causation

H. pylori condundrum and dual nature.

Your microbiome as an essential organ

Microbial genome is more important than DNA genome?

Bacterial Genes > Human Genes.

“an essential but largely ignored overlay”

“each body habitat harbors dominant signature taxa”

“interpersonal variation was significantly greater than intrapersonal variation”

“gut microbiota eventually converge toward an adultlike profile during the first year of life”

“host genotype had a large influence on gut microbiota composition, independent of litter and cohort effects”

“Microbiome profiling clearly has a role in personalized medicine that extends beyond the variation in drub-metabolizing enzymes”

“Studies also illustrate the potential of the microbiome as a disease marker.”

“intrapersonal variation in microbial community membership and structure between symmetric skin sites is lower than interpersonal variation, as determined by 16S rRNA gene sequencing”

Antibiotics bad bc 1) increase resistance of pathogens and 2) remove natural microbiome.

“prognostic value of microbiome markers”: ability to determine survive or not

(1)

“A primary goal of the Human Microbiome Project (HMP) was to provide a reference collection of 16S rRNA gene sequences collected from sites across the human body that would allow microbiologists to better associate changes in the microbiome with changes in health.”

“even with the considerable intra- and inter-personal variation in the human microbiome, this variation can be partitioned into community types that are predictive of each other and are likely the result of life history characteristics.”

“the community type at one body site was predictive of the community type at another body site.”

“detect associations between communities that had very different taxonomic compositions.”

“given the myriad permutations of genetics, life histories, behaviors, environments, and exposures, an individual’s microbiome is an emergent property whereby a potentially limitless number of microbial community structures can be distilled into a finite number of types. Knowledge of the factors that affect one’s community type profile will be critical as they continue to be associated with predisposition to diseases.”

(2)

Importance of Microbiome in Development

Ie max height is determined at a young age

Importance of microbes in pregnancy/infant health

Microbes in milk

Modern disinfection is harmful?

C Section babies lack microbes that have been *selected* for

Microbial poplns change over time.

Ie dramatic changes in height over a short period.

Combination of microbes and environment contribute to height

However, “microbial signature” is consistent.

“the aggregate genomes of gastrointestinal bacteria provide novel benefits by functioning as the third major genome in mammals along with the nuclear and mitochondrial genomes.”

“The microbiome harbors genes that code the components of many metabolic processes not found in mammalian cells but that are nonetheless essential for optimal health, such as the ability to degrade indigestible dietary components like fiber and plant cell wall polysaccharides”

“Since the well-being and phenotypic state of a host depends on the intimate association with its GI microbiota, it has been suggested that mammals can be considered as superorganisms, composed of an amalgam of both prokaryotic and eukaryotic cells”

“The inability of organisms to survive independently (GI microbiota) or to maintain normal health (mammalian hosts) is a strong indication of coevolved mutualism.”

“preweaned infants have simpler but more variable microbiota than weaned children or adults, who are more complex but also more uniform”

“the composition of the GI microbiota is strongly influenced by the host's diet.”

“The mutualistic relationship of the mammalian host with its GI microbiota is based on tolerance. Reduced or altered host tolerance to GI microorganisms can lead to inflammatory disorders such as inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS)”

“Probiotics are live microorganisms that when administered in adequate numbers confer a health benefit on the host. “

(3)

“One difficulty with studying these mechanisms in human subjects is the inherent baseline variability of the microbiota in different individuals.”

“The ability of the gut microbial community to recover to baseline following the cessation of antibiotic administration differed according to the antibiotic regimen administered. Severe antibiotic pressure resulted in reproducible, long-lasting alterations in the gut microbial community, including a decrease in overall diversity.”

“the community of indigenous microbes forms an ecological barrier that prevents the ingress of pathogenic microorganisms.”

“Anti- biotic disturbance of the normal community structure of the microbiota may allow the germination of environmentally acquired spores, with subsequent overgrowth of the pathogen and toxin production.”

“significant inter-individual variation in the indigenous microbiota (12, 13). This variation likely arises from the accumulated effects of genetic and environmental influences on the gut microbial community”

“Further- more, it is also assumed that the microbiota responds in a reproducible manner to the antibiotic administration, resulting in consistent changes in the structure and function of the microbiota that are responsible for the observed changes in the host response. These crucial assumptions have not been rigorously tested to date”

“Antibiotic treatment studies have shown that antibiotic-resistant bacterial pathogens can exploit innate immune deficits triggered by antibiotic administration”

“This high degree of similarity also provides evidence for the existence of community “assembly rules” that govern the establishment and stability of these microbial consortia.”

“an individual’s gut microbiota can have a relatively stable community composition over a period of months to years. These observations have led to the conclusion that the community of microbes in the gut is relatively resistant to perturbation by various ecological stressors. Subsequent environmental influences, including diet, host genetics, medication use, and exposure to infectious agents, can all influence the resultant microbial community”

“the gut microbial community exhibited resilience as the community structure shifted back toward the base- line state following cessation of the AMB treatment. However, the ability of this community to recover following antibiotic disturbance was not absolute. The administration of cefoperazone also caused dramatic shifts in community structure, but in this case, diversity did not recover even 6 weeks after the discontinuation of the drug. Rarefaction analysis revealed a persistent, significant decrease in overall species richness in the gut community following cefoperazone administration.”

“The ecological disturbance mediated by cefoperazone appears to have overcome community resilience, potentially due to different spectra of antimicrobial activity”

“colonization resistance,” the ability of the indigenous microbiota to prevent the ingress of pathogens into the gut community,”

(4)

“The species that make up these communities vary between hosts as a result of restricted migration of microorganisms between hosts and strong ecological interactions within hosts, as well as host variability in terms of diet, genotype and colonization history”

“Each community contains microorganisms from certain families and genera that are found in the same habitat in many or most individuals, although at the species and strain levels the microbiota of an individual can be as unique as a fingerprint”

“Evolution to increase mutualistic benefits has been called ‘partner fidelity feedback’, and it is strengthened if the same lineages of partners interact across multiple generations”

“Therefore, microorganisms are free to compete for resources in the gut, generating a robust and disease-resistant community, but are prevented (usually) from exploiting the host to obtain

additional resources.”

“Humans and their collective microbiota are segmented into many

local communities, each comprising an individual human with his or her symbionts. This ecological pattern, characterized by strong interactions within distinct local communities and limited interactions or migration between them, is described as a metacommunity. Another level of metacommunity organization exists because individual humans belong to social groups that tend to share a similar microbiota”

“Not only selection on community-level traits but also competition within the community and chance colonization events affect the structure of the microbiota”

“reflect a long history of stability in the types of microbial niche associated with terrestrial animals, together with factors (such as host heterogeneity and metacommunity structure) that promote diversification among organisms in similar niches.”

“Antibiotics can markedly affect the composition of the microbiota in the short term, with most (but not all) families and genera of gut micro organisms returning to typical levels within weeks of exposure. However, pathogens can exploit the reduced competitiveness of a community disturbed by antibiotics, thereby establishing themselves in the host”

(5)

“Although some of this variation can be explained by litter and cohort effects, individual host genotype had a measurable contribution”

“the composition of the adult gut microbiota varies dramatically from individual to individual, including differences in the relative ratios of dominant phyla and variation in genera and species found in an individual host (4). Once established, these compositional features are highly resilient to perturbation (5). Although the mechanism of this homeostasis is unknown, it suggests a “top down” model for assembly of the symbiotic microbial community that is largely determined by the host. ”

“In humans, this period of succession persists until 18–24moof age, when the gut microbiota attains its “adult-like” composition and begins to behave as a highly individualized climax community”

“By exerting top-down selection pressure, host genetic control would subdue microbial competition within the gut ecosystem to promote microbes that benefit the host at the cost of their own competitive fitness. This view is consistent with the suggestion that the adaptive immune system has specifically evolved invertebrates to regulate and maintain beneficial microbial communities (43).”

“the gut microbiota can now be viewed as an environmental factor that itself is controlled in part by host genetic factors and potentially by interactions between host and microbial genomes.”

(6)

Microbes must balance b/w cooperation and cheating to get ahead. Balance b/w own benefits and human body/community benefits.

Change in microbiome can be good for responding to a disease, but this loss/change in diversity makes future responses more difficult

Antibiotics as the “atomic bomb”

Short vs long, known vs unknown side effects

Antibiotics can cause permanent microbial popn change.

especially during crucial development stage.

Disappearing Microbiome

If disappearing is pathogenic 🡪 good. Beneficial/neutral 🡪 bad.

Microbes that assist/protect against allergies are being removed by antibiotics/disinfecting procedures.

Freq antibiotics/treatments increase harmful effects on natural microbiome.

Vicious cycle of relapses and more antibiotics

For example, one nosocomial strain (C. dificile) has evolved parallel strains bc of selection due to antibiotics. This is a problem bc it becomes resistant to many things.

A large volume of a single microbe does not mean it is essential. A small volume of a single microbe does not mean it is not essential.

Diversity essential to avoid extinction by allowing for a “margin of error”

Loss of “contingency” microbes 🡪 increased risk

Problem 1: increase in allergies

Problem 2: obesity

Use in farms to increase yield and decrease price

Increase in resistance w/o saving lives

Accumulation of antibiotics in food?

Antibiotics make kids “heavier” too?

Microbes that improve nutrition + antibiotics that make kids heavier have synergistic effects on weight/obesity.

Challenges to Solutions: Social

Social Pressures 🡪 overuse

Economic Pressures 🡪 delay in research

Social Impacts

Personal vs Institutional challenges

Cost vs effort by doctors

Influence of norms/dogma

Challeges: “technical”

It will be problem bc rate of resistance > discovery of new drugs

Solution 1:

Manipulating Microbes as treatment?

Can it be harmful?

What is the “normal” microbiome?

What beneficial microbes have already been lost?

Venezuela case

Probiotics. Can a pre-determined set of microbes help a personal case?

Example: manually inoculating c section babies

Solution 2:

French program to reduce dependency.

Antibiotics are not Automatic.

Antibiotics only when necessary.

“Furthermore, there is some evidence that decreasing antibiotic use can lower MRP rates [8]”

“France was also identified as the country with the highest antibiotic consumption in Europe [12] and one of the highest antimicrobial users worldwide. Thus, the French government initiated a long-term nationwide campaign to reduce antibiotic overuse and control the dissemination of resistant bacteria in the community. The national program, named ‘‘Keep Antibiotics Working,’’ was launched in 2001, targeting both the general public and health care professionals, to encourage surveillance of antibiotic use and resistance and to promote better-targeted antibiotic use”

“Our data show that the primary objective of the French national campaign was largely achieved, with a 30.1% decrease in antibiotic use in children,6 y old. This result is very encouraging, because a substantial proportion of antibiotic prescriptions for young children are unnecessary because of the viral origins of their infection [26].”

“a cause–effect relationship between the campaign ‘‘Antibiotics are not automatic’’ and decreased antibiotic use cannot be proved.”

“Second, we did not have access to information about the pathology for which antibiotics had been prescribed. In France, no information system exists that provides easy access to data linking drug use to a clinical condition”

(7) (7)

Decrease in numbers of prescriptions.

Multifaceted approach: cannot declare which factor was most effective and “give” that factor to other nations/programs

“the effect on antimicrobial resistance is still unclear and difficult to separate from the effect of the conjugate pneumococcal vaccine. “

“in countries with high baseline antibiotic use, sustained and multifaceted campaigns using mass media as well as targeting physicians can decrease antibiotic use substantially.”

(8)

“Infections caused by highly drug- resistant pneumococcal isolates are associated with higher rates of treatment failure and/or mortality than are infections due to drug-susceptible strains.”

“Interventions were centered around an extensive information campaign that used the message “antibiotics are not like other drugs,” which was aimed at physicians, pharmacists, parents, and children, and a children’s game called “In the Pursuit of the Lost Bacteria” was created and distributed to all kindergartens to heighten awareness of the problem of appropriate”

“the rate of S. pneumoniae colonization was significantly lower in the prescription-reduction group than in the control group”

“The results showed that a 4-month intensive educational strategy was able to reduce antibiotic use and that such a modification rapidly leads to substantially decreased rates of PNSP carriage. This is, to our knowledge, the first population-based study to demonstrate that, when antibiotic exposure is reduced, antibiotic-susceptible strains recover a survival advantage (regardless of serotype) and subsequently tend to once again be- come more-dominant human colonizers.”

“Our observations suggest that, for populations whose rate of antibiotic exposure has been reduced, antibiotic-susceptible organisms may recover a survival advantage and may subsequently tend to become more-dominant human colonizers,”

“The prescription-reduction group started at much higher rates of antibiotic use and PNSP, so it was an “easier target.” Nevertheless, the reduction in the rate of antibiotic use was very substantial in this group. Surprisingly, the dose-duration group had a similar slope in the decrease, without clear explanation. These results do not allow one to predict the long-term impact of decreased antibiotic use on PNSP colonization and, in particular, on the possibility of a decrease in the rate of PNSP colonization.”

(9)

Solution: narrow focus meds + faster diagnoses

“Vaccines can reduce the prevalence of resistance by reducing the need for antimicrobial use and can reduce its impact by reducing the total number of cases.”

“Because much selection for resistance is due to selection on bystander members of the normal flora, vaccination can reduce pressure for resistance even in pathogens not included in the vaccine”

“Avoiding antibiotics reduces opportunities to select resistant variants of the targeted pathogen, and of other, “bystander” species that are susceptible to the antibiotic (10).”

“amplified by the indirect protection, or herd immunity (11), that results when vaccinated individuals do not themselves become infected or colonized, and hence do not transmit the pathogen to others. In this way, infections, resistant infections, and antimicrobial use can be reduced not only in vaccinated individuals but also in their contacts”

“targeting vaccines againstresistant strains or even against resistance determinants them- selves may be an effective way to counteract selection pressure for antimicrobial resistance”

“antiresistance vaccines should be more effective against drug-resistant strains than against drug-susceptible strains, either by specifically targeting resistant alleles of a con- served protein (such as a penicillin-binding protein in bacteria or neuraminidase in influenza virus) or by targeting proteins uniquely present in resistant isolates”

“Designing a vaccine to specifically target resistance determinants or resistant lineages is in early stages, but the idea may be promising (83). The first step is clearly to explore in multiple systems whether resistance determinants, or antigens strongly associated with them, can be immunogenic and protective.”

“theoretical prediction that even very weak selective pressure exerted by a vaccine could shift the balance against resistant strains”

(10)

“First, design an inhibitor against an enzyme or process that is only found in the targeted pathogen. This approach has the challenge of identifying a novel, essential target in each pathogen. A second approach circumvents this issue and utilizes structure-based design to build high-affinity inhibitors that are optimized against the specific version of the drug target expressed in the pathogen.”

“treatment caused minimal effects on both the bacterial abundance and composition of the gut microbiome illustrating that pathogen-selective antibiotics can be developed to minimize disturbances to the microbiome.”

“By day 12, the S24-7 family had recovered to pre-treatment levels in the Debio 1452-treated mice, and the gut composition of Debio 1452-treated mice was indistinguishable from untreated mice during the entire recovery phase (day 12-37) showing that this FabI inhibitor did not have a lasting effect on the microbiome”

(11)

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