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Trajectories of genetics, 150 years after Mendel/Trajectoires de la génétique, 150 ans après Mendel

The human gut microbiome impacts health and disease

Le microbiote intestinal humain influe sur la santé et la maladie

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ABSTRACT

The human gut microbiome can now be characterized in unprecedented detail by an approach based on high-throughput sequencing of total stool DNA, that we name quantitative metagenomics. Central to the approach is a catalog that lists all the genes of intestinal microbes that are known – 9.9 millions, identified by the analysis of 1267 stool samples. Beyond the gene list, genetic units that carry them begun to be known; many of these correspond to bacterial species that were never isolated and cultured yet. Quantitative metagenomics allows developing powerful algorithms to diagnose a disease, monitor patients and identify individuals at risk to progress towards a disease. This lays ground for developing new approaches to better restore and even preserve the health by modulation of the altered microbiome, which contributes to promote or aggravate a disease.

Mots clés :
Métagénomique quantitative
Catalogue des gènes microbiens
Communautés microbiennes
Dysbiose
Prévention des maladies chroniques

RÉSUMÉ

Le microbiote intestinal humain peut maintenant être caractérisé en détail par une approche basée sur le séquençage à haut débit de l'ADN total des selles, que nous appelons métagénomique quantitative. Le cœur de l'approche est un catalogue qui répertorie tous les gènes des microbes intestinaux qui sont connus – 9,9 millions, identifiés par l'analyse de 1267 échantillons de selles. Au-delà de la liste des gènes, les unités génétiques qui les portent commencent à être connues ; beaucoup d'entre elles correspondent à des espèces bactériennes qui n'ont jamais été isolées et encore moins cultivées. La métagénomique quantitative permet de développer des algorithmes puissants pour diagnostiquer une maladie, de surveiller les patients, ainsi que d'identifier les personnes qui présentent un risque de développer une maladie. Cela jette les bases du développement de nouvelles approches pour mieux restaurer et même préserver la santé par modulation d'un microbiote altéré qui contribue à favoriser ou à aggraver une maladie.

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1. Introduction

The human gut microbiome can be thought of as our neglected organ [1]. It is comprised of more microbial cells than the remainder of our body, can weigh two kilograms, more than most other organs, and has a considerable metabolic activity. The microbial organ is not indispensible, as germ-free animals are viable. However, their development is impacted as their gastrointestinal tract, immune system and even brain are not fully mature, and we do not know whether their life outside of the strictly sterile conditions where they are maintained would be possible. The microbial communities that compose the neglected organ are altered in numerous diseases, in particular the chronic ones, which are constantly increasing in the industrialized societies [2]. This raises the possibility that the organ may play a role in these diseases. But why has it remained neglected, while it clearly should have been investigated? A simple answer is that there were no appropriate tools to study it. A traditional way to characterize microbial communities is to enumerate the species that they contain by culturing them in appropriate media, but for most of the microbial species from our gut we still do not have such media and do not know how to grow them reliably. The situation has changed by the advent of molecular methods precise enough to detect most of the species and determine their abundance.

2. Quantitative metagenomics for microbiome assessment

The method has been developed in the European MetaHIT consortium (http://www.metahit.eu/), operational between 2008 and 2012, and relies on the advent of new generation sequencing (NGS) techniques, capable of generating millions of sequencing reads in parallel and the numerical tools capable of handling Big Data (Fig. 1). A catalog listing the genes of intestinal microbes is central to the approach. It is used to determine the presence and the abundance of each gene in any sample under study, that is, the gene profile of any individual at a given point in time. A view of the microbiome of unprecedented precision is thus obtained. Comparisons of microbiomes (gene profiles) of different individuals, say patients and healthy controls, reveal the genes and species that distinguish them, by their presence or their abundance. The contrasting genes and species can be used, in turn, to develop powerful diagnostic and even prognostic algorithms of clinical relevance.

The first gene catalog was established in 2010, ten years after the sequencing of the human genome, by the analysis of 124 individuals of European origin [3]. It contains 3.3 million genes (> 99% bacterial, remainder of viral and eukaryote origin), 150 times more than our own genome, and was dubbed *our other genome*. An updated version of the catalog was released four years later. It contains 9.9 million genes, found by analyzing ten times more individuals from three continents (Europe, Asia and North America), and the sequenced reference genomes of cultured gut species [4]. Notably, the number of genes found in at least 5% of analyzed individuals increase little with each additional sample, whereas that of genes harbored by only a few individuals continue to increase, without sign of saturation. The former may approximate "core" components of the microbiome, whereas the latter can be viewed as "individualized" parts, corresponding likely, on the one hand, to transient rather than to resident gut

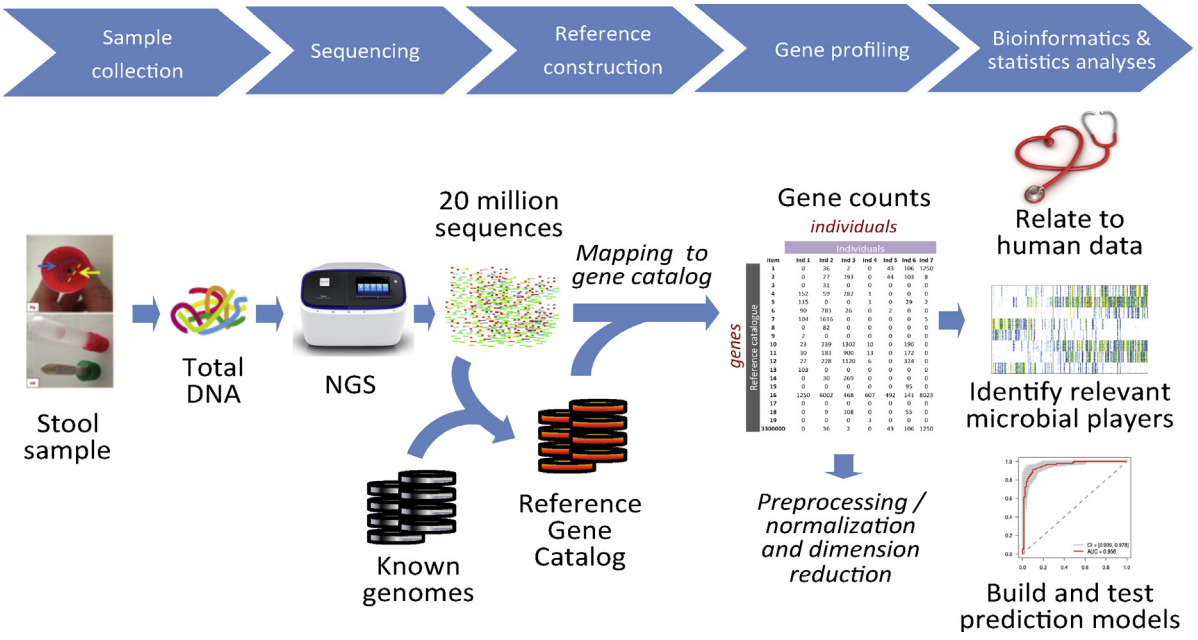

Fig. 1. Quantitative metagenomics for the characterization of the human gut microbiome. Total DNA is extracted from a stool sample, sequenced to generate millions of reads; the reads are mapped to a reference catalog that lists all the known gut microbial genes, and a gene count table is generated for each sample. The counts are converted into gene profiles, the profiles are related to bioclinical data, and the models of clinical relevance are generated.

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