Phage sensitivity and CRISPR profiles of Escherichia coli strains isolated from the gut of COPSAC2010 cohort children

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Résumé

In light of its crucial role in human health, the gut microbiota has been extensively studied in the last decade. A very diverse and abundant population of phages also colonizes the gut and is referred to as the gut virome. However, the literature on the gut virome is largely centered around viruses fortuitously sampled through metagenome analyses mostly targeted at the bacteria. Techniques for extracting and sequencing viral particles from such complex environments are also still embryonic. Thus, it remains challenging to explain the roles of the phages, the identity of their hosts and their interactions in the gut. CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) loci, together with their *cas* genes (CRISPR associated genes) are found in nearly half of the bacterial genomes sequenced so far. They provide adaptive immunity against invading genetic elements by incorporating short DNA sequences in the locus, called spacers, in an orderly fashion. These spacers often originate from the phage genome and allow the bacterium to block a subsequent infection. The integration of new spacers is primarily localized on one end of the locus, similar to adding a new page to a book. This characteristic, combined with the rapidly-evolving structure of the locus, can serve as a molecular archive of past phage-bacteria interactions. We sequenced the two most active CRISPR loci of 1871 *Escherichia coli* isolates originating from 700 children and their mothers enrolled into the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) cohort, sampled during the third trimester (vaginal samples) and 1 week, 1 month and 1 year after birth (feces samples). By looking at the spacers content of the loci, we attributed a CRISPR signature for each isolate. We observed a clear bacterial transfer from the mother to the child and occasional spacers acquisition and deletion over time. Total gut virome has also been extracted and metavirome sequenced from a subset of the cohort. 16 of all 1763 distinct spacers matched a sequence retrieved from the virome. At this time, we have challenged 1769 *E. coli* isolates with 16 well-characterized coliphages to determine their phage sensitivity profile. Some bacteria were immune to all phages, while others were sensitive to more than six distantly related phages. Interestingly, we found no correlation between the CRISPR signature and the phage sensitivity profile, emphasizing the idea that other defense mechanisms are at play for *E. coli* to defend themselves against phages in the gut ecosystem.

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