Slide 1 : Overview

This presentation will focus on the interaction of phages present in the gut and the impact it will have on human health.

Slide 2 : Introduction

1.

Microbes present in and on us play a significant role in our health and well-being.

These microorganisms provide a range of essential functions:

From helping us to digest food, to conditioning our immune system, and providing protection from invading pathogens.

2.

The collection of microorganisms that grow and live on the human skin, or in the human gut, blood or respiratory tract is called the microbiota.

This microbiota also includes bacterial viruses, the bacteriophages.

3.

When talking about the total population of viruses, or virus-like particles, associated with the microbial community, we call this the virome.

If we take the bacterial dominance of bacteria in the gut microbiota into account, it is clear that the gut virome is dominated by prokaryotic viruses. The exact size of the mammalian virome is not known.

Slide 3: Accessing and analyzing the human gut virome

1.

To study the composition of the gut virome, culture based methods, high resolution microscopy and metagenomic analysis are mainly used.

2.

The culture based techniques involve the isolation of phages from the environment using a specific bacterial host.

Unfortunately this method is limited by the inability to culture more than 99 % of the bacterial species found in the environment, in this case the gut.

3.

High resolution microscopy mainly focusses on the absence or presence of the viral particle or its morphology, but does not give any information about its host specificity or how many different phages are present. The main technique used here is electron microscopy, which gives clear information about the phage morphology.

4.

Metagenomic analysis makes use of high throughput sequencing and associated bioinformatical methods to obtain an in-depth view of the structure and functioning of these viral communities.

The first step in this method is the isolation of virus-like particles. We talk about virus-like particles because we only know about their existence through their genomic data, but we do not have any biological information as we do not know which bacterial host they use to amplify.

Using a bioinformatical approach that assumes that sequences that are repeatedly found in different metagenomes are most likely to be part of the same genome, revealed the existence of a highly abundant 92 kb phage in multiple individuals, called the crass phage.

This method bioinformatical method is called the cross-assembly method.

Slide 4: Effect of phages in the gut on human health

1.

One of the most densely populated areas of the human body is the gastrointestinal tract, which provides a heterogeneous surface area for microbial life.

The human gut is estimated to contain between 30 and 400 trillion microorganisms.

The number of bacteria vary extensively across the length of the gastrointestinal tract.

Where there are bacteria, there are viruses. And the human gut virome is closely related to dietary habits and the surrounding environment.

2.

The gut virome is largely dominated by lysogenic bacteria.

And studies have shown that individuals who share similar dietary habits have similar viral populations in their gut virome. Food can thus be considered as a common reservoir of viruses or as a tool that carries a selective pressure.

Slide 5: Effect of phages in the gut on human health

1.

The human gut contains a mucosal layer. This layer has two functions.

The first function is that the mucosal layer forms a protective barrier, where the pathogenic bacteria are hindered to invade the human cells.

The second function of this layer form a habitat for resident commensal bacteria and phages.

These resident phages form a non-host derived anti-microbial defense, through actively lysing their target bacteria.

Slide 6: Interaction of phages with the human immune system

1.

Besides regulating the bacterial microbiome, the virome can also directly interact with the human immune system.

It has been shown that phages can accumulate in cancer tissues and even inhibit tumor growth. The binding of phages to cancer cells has been shown in *in vitro* and *in vivo* studies.

Furthermore it has been shown that phages can bind to the plasma membrane of lymphocytes. This interaction occurs through a protein on the plasma membrane, called beta three integrin, with a phage protein containing a three amino acids, or a tripeptide motif, Lysin-Glycin-Aspartic acid.

2.

The oral administration of phages in animals has shown that these phages can enter the blood, this indicated that there is a mechanism whereby phage translocate from the gut towards the blood.

Once the phages enter the blood, they are able to induce innate and adaptive immune responses.

These interactions with the immune systems are not necessarily negative for the mammalian host.

Slide 7: Interaction of phages with the human immune system

1.

On one hand phages work together with the mammalian immune system in order to completely remove the bacterial infection, in a process called neutrophil-phage synergy.

Neutrophils are cells that form a part of the innate immune system, and play crucial roles in the removal of pathogens.

2.

On the other hand, phages are able to reduce or escape the innate immune response. This is an important property of the phages because it enables the phage to be present in the blood without inducing an immune response or being rapidly removed.

3.

Because phages are basically tightly packed DNA or RNA with a protein coat, they can easily lead to the production of antibodies in the blood.

These antibodies will inactivate the phage making it no longer possible for the phage to infect its bacterial host.

4.

Knowing that phages do not induce an inflammatory response but lead to the production of an antibody response, phage phi X 174 has been used to diagnose and monitor immune deficiencies.