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Bdellovibrio bacteriovorus como posible agente de control biológico

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Abstract

Within ecosystems there is a hierarchical form of survival, where the predator hunts its prey for that purpose. From aquatic environments, to terrestrial ones, but we rarely turn to see the microscopic world of bacteria where in the same way these living beings look for a way of survival and some of these microorganisms develop in a predatory way. In this review we focus on Bdellovibrio bacteriovorus HD100, which belongs to the Bdellovibrio group and organisms similar to BALOs (Bdellovibrio and like organisms), which have different forms of attack and depend on a prey for their survival, growth and reproduction. These Bdellovibrio spp can be used as possible biological control agents against pathogenic bacteria resistant to antibiotics.

Prey, Predator, Bdellovibrio

Resumen

Dentro de los ecosistemas hay una forma jerarquizada de supervivencia, en donde el depredador caza a su presa con dicho fin. Desde ambientes acuáticos, hasta los terrestres, pero pocas veces volteamos a ver el microscópico mundo de las bacterias en donde de la misma manera estos seres vivos buscan una manera de supervivencia y algunos de estos microorganismos se desarrollan de manera depredadora. En esta revisión nos enfocamos a Bdellovibrio bacteriovorus HD100, el cual pertene al grupo Bdellovibrio y organismos similares a BALOs (Bdellovibrio and like organisms), los cuales tienen diversas formas de ataque y dependen de una presa para su supervivencia, crecimiento y reproducción. Estos Bdellovibrio spp pueden ser empleados como posibles agentes de control biológico contra bacterias patogenas resistentes a antibióticos.

Presa, Depredador, Bdellovibrio

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Introduction

In a pluribiótico planet where the alimentary chain forces to form a symbiosis, sometimes, this ends up forming an environment of predation.

From large mammals to microorganisms, which seek to survive. To understand this, let's situate ourselves in a hostile environment, where the hunter or predator needs food to get the necessary nutrients, this food is only obtained by another living being that is known as prey. Thus, sharks are the marine predators par excellence, the big cats are in their ecosystem and humans are the biggest predators in the world. However, in the microscopic world, there are also predatory bacteria, some need a host to survive. The first bacteria classified in this way were the myxobacteria, since then, several studies and reports have been made about the predatory bacteria, with what has been learned about their environmental consequences, their ways of hunting and even possible applications. Clearly, each predatory bacterium has its own way of hunting, as well as a different lifestyle.

Methodology

- Sample collections were obtained preferably from soil near water tanks.
- To isolate the bacteria it is necessary to perform a pre-enrichment stage, preparing a 1: 2 mixture of 10 g of soil with sterile water or 50 ml of aquatic sample, and centrifuge 5 min at 500 xg, discarding the pellet formed, the supernatant is centrifuged 20 min at 27,000 xg, but at this point, the supernatant is decanted and the resulting pellet is dissolved in a few drops of HM cold buffer, finally it is passed through a 1.2 μm filter keeping at 4 ° C for a few days.
- If necessary due to contamination, it should be filtered again on a 0.45 μm filter, although this could reduce the performance of BALOs.
- The agar with the prey is prepared separately in a medium containing the HM buffer. Allowing this layer to solidify and finally, mix and incubate at 30 ° C for 3 to 8 days, continuously checking the medium, until approximately 5 days when lysis is observed.
- It is cut around 1 millimeter, in the lysis area and aspirated and then resuspended in 0.5 ml of HM buffer. Let it rest for a few minutes and then shake.
- Moving cells can be observed by means of a phase contrast microscope.
- Repeat steps 3 through 6 twice to obtain pure cultures.
- To obtain the predator, 10 ml of the culture is centrifuged at 3000 RPM for 20 min and filtered through a 0.45 or 0.25 μm pore.
- Centrifuge to obtain a pellet with the predator.
- After this the DNA can be extracted, amplified by PCR and sequenced by means of 16S rRNA.

Classification of BALOs and BALO Diagnostics by PCR

- Filter the BALO suspension twice by a 0.45 μm micropore, centrifuge for 10 minutes at 10,000 x g at 4 ° C and resuspend in sterile water at 1/10 volume.
- Extract the DNA according to the standard protocol of Moore and Dowhan, 2002, or with an extraction kit.
- Cool on ice, and add DMSO to obtain a final concentration of 10%.
- On the other hand, prepare the PCR mixture in the following manner in a 50 μL tube.

I. DNA, 10 ng on 1 o 2 μL.
II. 3 Mm $MgCl_2$
III. 20 μM de dNTPs
IV. Buffer 1X
V. 1.25 u Taq DNA polymerase
VI. 1 μM of each first. (63 F 5´ CAGGCCTAACACATGCAAGTC 3´ and 1278R 5´CGGTGTGTACAAGGCCCGGGAACG 3´)
VII. 12.5 μg of BSA
VIII. Water mili-Q degree PCR cbp. 50 μL.

- Amplify using the following protocol for the Thermal Cycler.

I. 4 min at 94 ° C for initial denaturation.
II. 35 ciclos de:
III. 1 min at 94 ° C denaturation
IV. 1 min at 50 ° C alignment
V. 1 min at 72 ° C extension
VI. 5 min at 72 ° C for the final extension

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– Verify the presence of the PCR product running 5 μL in 1% agarose gel in TAE.
– Sequence the PCR product

Results

Predatory bacteria

Due to the behavior of bacteria there is controversy regarding the classification of this type of cells as predators or parasitic, we must put in context that the term predator should be used for that which has a prey and hunting for various purposes, mainly to get nutrients while parasitic cells are those that form symbiosis with its host without kill (Perez et al., 2016).

These bacteria have a wide distribution ranging from aquatic environments, to extreme habitats with high concentrations of sulfates that are reduced to methane by some bacteria such as Desulfovibrio, Desulfobacter and Desulfobacterium (Sahaniuk et al., 2004) (Kevorkian et al., 2018) . These have co-evolved with prey bacteria, however we can see that within the applications of these predatory cells do not spread beyond the environment where they are, that is, they are not pathogenic for it (Tyson and Sockett, 2017).

Predation forms

There are several forms of predation, which can be classified into three main groups, considering previous knowledge of this type of bacteria (Perez et al., 2016).

Epibiotic depredation

In this strategy the predator contacting the cell without an invasion of the host, the predatory bacteria remain bound prey from the outer membrane and from there degrade cell wall to consume. Some examples of predators are Vampirococcus, Micavibrio and Bdellovibrio exovorus (Martin, 2002).

Endobiotic predation

It is also known as direct invasion, since in this form of predation, the bacterium penetrates its prey and invades the periplasm or cytoplasm in order to feed, grow and reproduce until it lyses the host cell to begin its cycle again, a The main example is B. bacteriovorus (Pérez et al., 2016).

Predation in group

As the name implies, are those bacteria that have the strategy of preying on their prey in groups.

In this tactic predatory cells secrete compounds which kill and decompose nearby prey, these products can bind to the surface of the predator or, they are embedded in the extracellular matrix in this category is found to Mixococcus xanthus and some bacteria of the Lysobacter genus spp. (Velicer & Mendes-Soares, 2009) (Livingstone et al., 2018). There are other groups of unicellular or multicellular organisms such as marine algae that produce enzymes capable of attacking some human pathogens and also to combat some pathogens of plants such as the potato blight P. infestans (Bartulos et al., 2018).

BALOs

The group of Gram-negative bacteria predators of other Gram-negative bacteria, are known as BALOs or bacteria similar to Bdellovibrio by its acronym in English "Bdellovibrio and Like Organisms" (Chen et al., 2011).

These organisms typically have a double lifestyle, one external to the prey cell, usually the recognition phase and another within the host, where it carries out its feeding, growth, development and reproduction, by multiple fission (Jurkevitch and Jacquet , 2017).These organisms include the genus Micavibrio and the families known as: Bdellovibrionaceae (Stolp and Starr, 1963). Bacteriovoracaceae (Baer et al., 2000), Peredibacteraceae (Piñeiro et al., 2008) and Halobacteriovoraceae (Koval et al., 2015). Thanks to the nature of these organisms and their hosts, as well as to biotechnology, an application approach can be given to the BALOs to study them from the environmental impact to their applications in agriculture, industry, as well as clinical issues (Jurkevitch and Jacquet, 2017) (Kevorkian et al., 2018).

Bdellovibrio bacteriovorus

In an effort to meet a species of BALOs, we focused on B. bacteriovorus, which comes from the Bdellovibrionaceae family, which was first described by Starr and Stolp as a predatory, ectoparasitic and bacteriolytic bacterium, since it lysed Pseudomonas in soil samples (Stolp and Starr, .1963).

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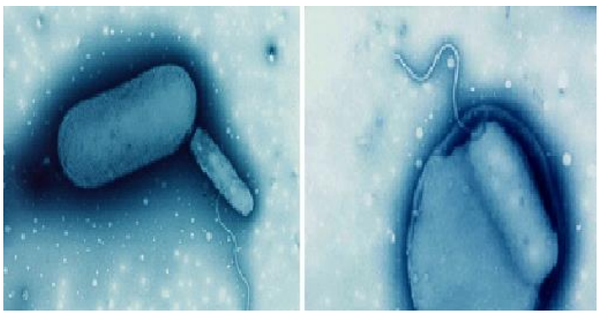
In later studies they demonstrate the second phase of their life cycle, which consists of penetrating the prey cell in order to grow parasitically (Starr and Baigent, 1966).



A B

Figure 1 Electron micrograph of B. bacteriovorus predating E. Coli, in figure A. we observe the prey binding phase, while in figure B we can observe the intracellular phase, (Lamber et al., 2006)

It is a Gram negative bacterium, obligatory aerobic, uniflagelada whose flagellum measures near 50 μm, which gives motility to the cell, of the class Deltaproteobacteria, this flagellum is lost when entering its prey (Sockett, 2009), without However, in strains such as HD100, it has been shown that the flagellum sometimes fails (Lamber et al., 2006).

To exemplify in more detail, strains for this organism have been identified as strain HD100, which is described as dependent hosts (HD), where their dimensions were discovered, which are approximately between 0.2-0.5 μm wide and 0.5-2.5 μm long, its genome is 37.82950 bp, and it codified for 3584 proteins (Rendulic, 2004), Figure 2.

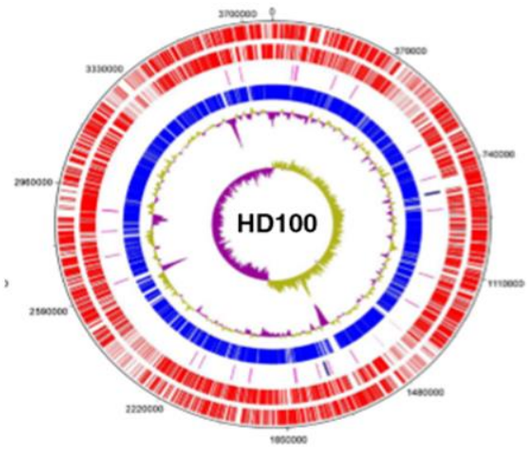


Figure 2 This image shows the circular genome of B. bacteriovorus HD100. Image taken from (Hobley et al., 2012)

It is ubiquitous and has been isolated from various habitats such as freshwater, wastewater, soil and mammalian intestines (Feng et al., 2016) proteins (Rendulic, 2004) (Atterbury et al., 2011). It is a host-dependent bacterium, because it needs a prey cell or host for its growth, it seeks to obtain a place in the periplasmic space of the bacteria Gram-negative prey forming a bdelloplasto, which allows a balance to be able to take the nutrients from its host (Willis et al., 2016). It has also been possible to develop an independent growth phase of the host achieved in laboratory conditions (Sockett, 2009).

Thus, we can say that its life cycle consists of eight stages; 1) B. bacteriovorus swims freely with its flagellum in the middle, 2) later when the bacterium finds its prey, collides and joins it and remains in a "recognition" stage, 3) in stage 3, Bdellovibrio generates an opening between the outer membrane of the prey cell, and the peptidoglycan layer performing mechanical movements on its own axis, which is resealed when the predator enters, in this stage B. bacteriovorus detaches from its flagellum upon entering to the periplasm of the dam, 4) DNA replication and synthesis of biopolymerases begins, 5) Once it is in the periplasm, Bdellovibrio forms a structure called bdelloplasto, 6) The filaments of the predator have grown several times their size and begin to form a wall, 7) Bdellovibrio becomes a flagellated cell and lists again, at this point, 8) Finally, the predator produces hydrolytic enzymes in order to dissolve the peptide layer Doglicane and the outer membrane of the cell prey to release progeny proteins (Rendulic, 2004) (Kuru et al., 2018), Figure 3.

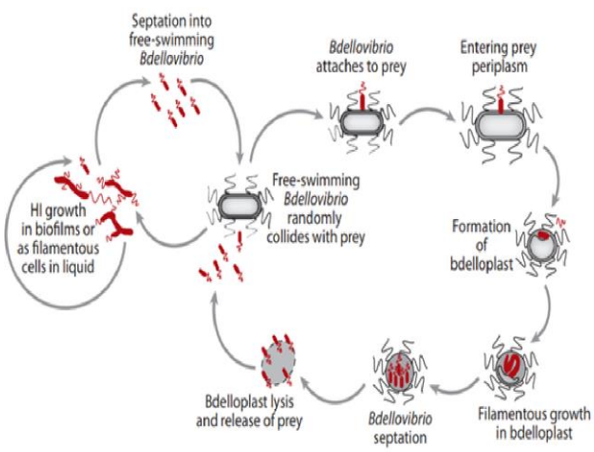


Figure 3 Image taken from the Sockett 2009. doi: 10.1146 / annurev.micro.091208.073346 where the life cycle of Bdellovibrio bacteriovorus is illustrated (Sockett, 2009).

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Likewise, through the study of the genome of Bdellovibrio bacteriovorus it has been possible to understand part of the process of interaction with its host, from knowing the genes that encode certain enzymes and the function they perform, Table 1.

Family	Bdellovibrionaceae
Species	*B. bacteriovorus*
Type of first isolated sample	Oil
Dam of choice	Gram negative
Genome size	3,782,950 pb
Content of G + C in DNA	50.6 %
Content of G + C that encode	50.4 %
OrFs	3584
RNAr operons	2
RNAr genes	36
Transposons	4
Regions encoding hydrolytic enzymes:	150 proteases
	20 DNAsas
	9 RNAsas
	10 Glicanasas
	15 Lipasas
	Otras 89

Table 1 Diagram of Bdellovibrio Bacteriovorus HD100

* Base pairs
** Open reading frames
*** Ribosomal RNA
**** Transfer RNA

It is thought that its high content of GC over the other BALOs is due to the microbiota of the environment where it is located, so the first isolate obtained from soil samples, where the genomes of the prey bacteria have rich regions in GC content in their DNA, so the transfer of predator-prey genes probably provided that result (Rendulic, 2004).

Discussions

As we can see, this predator focuses on its prey and at the moment has not been shown to have a negative influence on the environment around it. From this we can take advantage in various fields of study as we will analyze below. On the one hand, (Feng et al., 2016), they found B. bacteriovorus strain UP in a wastewater treatment plant in Singapore, where this bacterium was found to be predatory of planktonic species and species with biofilms, an interesting result it was the decrease of prey cells, which showed a decrease in predatory cells, a result that they had previously tested (Chu and Zhu 2010), by placing B. bacteriovorus C-1 in the presence of Aeromonas hydrophila, this result although it would seem Obviously, it shows us that different strains of Bdellovibrio are specific for a given prey (Feng et al., 2016).

In a study conducted by (Willis et al., 2016), focused on the veterinary-preclinical biomedical area injected Bdellovibrio in larvae of zebrafish (Danio rerio) infected with a strain of Shigella flexneri resistant to antibiotic and pathogenic to humans, where showed that Bdellovibrio can remain in vivo inside Danio rerio, without causing pathogenic damage in the larva, but it was observed predation in Shigella, when injecting a lethal dose, which denoted survival of the larvae of Danio rerio. The immune system of this fish, properly constituted by neutrophils and macrophages, gets rid of the predator in a sufficient time, once fulfilled its function.

However, a better effect of Bdellovibrio with immunosuppressed fish was observed, for obvious reasons, the predator had more time to fulfill its function (Willis et al., 2016).

From this we can rescue two things, the study argues that the immune system of the fish achieves, end with Bdellovibrio allowing time for the bacteria to deprecate Shigella.

However, in immunosuppressed fish this bacterium has more efficient predation, which may give rise to to more studies prior to a clinical study, however, the fact that bdellovibrio is a dependent predator, should die when there are no more prey, so if bdellovibrio persists inside the primary host, in this case Danio rerio, it should be look for, what is the underlying source of prey for which this bacterium remains.

In zootechnical veterinary medicine several studies have been carried out as they are in chickens and cattle, and even in rats, where Bdellovibrio has been exposed to pathogenic agents such as E. coli and Salmonella (Atterbury et al., 2011) (Boileau et al., 2011) (Shatzkes et al., 2017) .

For the chickens, when feeding the predatory cell, it was shown that Salmonella was not expressed, since it served as a host for B. bacteriovorus, there was no contamination of the chickens' environment with the bacteria and the life expectancy of the birds was improved. cattle were studied to study Bdellovibrio strain 109J as a predator of Moraxella bovis bacterium that causes bovine infectious keratoconjunctivitis, to reach a conclusion in vitro studies and subsequently in vivo were made to determine that B. bacteriovorus has potential as an effective bacterial control against M. Bovis (Boileau et al., 2011).

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Likewise, several investigations have been made to know the effect of B. bacteriovorus in combination with some substances, such as (Im et al., 2017), in their study with violacein, a Gram-positive antibiotic where they showed synergy when used with the predatory bacteria of Gram negative, obtaining results of 19% and 68%, of effectiveness being used separately for each type of bacteria, however, when this combination was used, they gave up to 99.98% effectiveness in an in vitro medium (Im et al., 2017).

Among other applications, preclinical tests have been carried out (Baker et al., 2017) and clinical studies as reviewed by (Lebba et al., 2013), where the first focuses on an in vitro environment to know the viability of our predator in question, demonstrating in a buffer at body temperature the development of a pathogenic bacterium, in this case Klebsiella pneumoniae, same as when using B. bacteriovorus HD100, a remarkable decrease of the prey cell was observed.

In the study conducted by (Lebba et al., 2013), faecal samples from pediatrics found that our predator was being studied in healthy patients, while in patients with celiac disease the presence of Bdellovibrio was considerably reduced, which appeared to be associated with mucosa.

Therefore, in some studies, this bacterium is proposed as a bactericidal agent or "live antibiotic" (Harini et al., 2013) (Negus et al., 2017). However, we must learn to direct it, since the strains for each predator have not been detected, as Baker who talks about the strain HD100 preying on K. pneumoniae, when it has been found that this strain is also predator of E. coli, or the strains are multi-predators, which would lead to new studies to check if there are collateral damages due to the use of this bacterium because it could possibly be preying on other bacteria of the human microbiota, since as mentioned in the study by Lebba et al. ., 2013, the predator has been found in the microbiota of healthy pediatrics (Baker et al., 2017).

It is important the role of Bdellovibrio in eliminating certain pathogens and that could probably act as potential prophylactic or therapeutic agents to fight infections, however many studies are still needed (Tester And Al-Ghazzewi, 2018).

Conclusions

Bdellovibrio bacteriovorus is an antimicrobial agent that can be isolated from diverse aquatic environments, this can have different applications, in the medical or clinical area, as probiotic in humans or combating pathogens resistant to multi-drugs, as an environmental bioremediating agent, as an agent of biological control of insect pests, in veterinary, among other applications. The role of Bdellovibrio in eliminating certain pathogens and that could probably act as prophylactic or therapeutic agents to fight infections is important, however, many studies are still needed.

Finally, studies could be carried out using biotechnological tools, on the interactions between the predator and its prey, tracking genes of specific interaction and looking for associations that do not affect the human microbiota of healthy individuals.

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