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Predicting the Future: Phage Therapy

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BACTERIAL pathogens have a major role in human disease and cause different symptoms in all human organs. In 21 century antibiotic resistance is widespread and causes mortal disease. Phages or bacteriophages are kinds of viruses that attack bacterial cells and are ordered into one phylum which is divided into three families: myoviridae, podoviridae, and siphoviridae. Phages have a triple role including (1) pseudovirion (bacterial gene in virus envelop that delivered pathogen gene), (2) virus that eliminates the bacterial cell, and (3) silent infection. Phage has three major sections: Head, neck, and tail. The attack begins with the attachment of the virus to the bacterial cell surface. The most phage receptor is presented in cell surface and has many roles in different bacteria. On the other hand, phage should be pure and removed all contamination to avoid an immune reaction. Phage can only affect bacterial cells and don't have collateral damage to eukaryotic cells. In addition, phage display is a hopeful method for treatment, detect and cure of many diseases. In this review, we try to show the role of phages in treating some diseases and detection by phage display method.

Keywords: Phage, Cure, Detection.

Introduction

The phages are most abundant organism in earth [1] and for this reason it is simple to isolated phage against bacterial cell. Phage classified based on shaped, genome sized, capsid size and genome type [2] . Phage like other antibiotic need to reach to bacterial cell in sufficient dose[3] . On the other hand phage has a different specificity: widespread and narrow host range [4]. Usually broad host phage isolated from aquatic sample [5] and maybe rapidly isolated from environment [6]. Phage can burst bacterial cell in different mechanism from other antibiotic without collateral damage to microbial flora [7], (Table 1).

Phage receptor

Lipopolysaccharide (LPS) acts as a phage receptors in Gram negative bacteria [16] . Phage that adsorb to smooth LPS is narrow host range, in contrast in rough LPS is a broad host range. ompA is a structural protein that involved in phage receptor and conjugation [16]. Teichoic acid and Muramic acid are crucial for phage adsorption in Gram positive bacteria[17].

Phage replication and enzyme

Phages can be categorized into Lytic, chronic and Lysogenic [18]. After the injection of nucleic acid into the bacterial cell, Lytic phages rapidly replicate and cause the release of virion through the bacterial cell bursts. Lysogenic pathways:

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insert a nucleic acid into host cell genome, where by their new replication of bacterial cell the phage transferred to daughter cell. Chronic pathway similar to lytic phage replicated but in slow mode that don't burst the bacterial cell [19]. Phage has an endolysins that attach to specific peptidoglycan bond and cleavage them to release new virion to the nature [20]. There are two ways to destroys peptidoglycans: 1) in large DNA phage has a lysins that attach to peptidoglycan bond and destroyed them, 2) in small RNA and DNA phage code protein that interfere with peptidoglycan synthetic pathway[21] .[see Figure 1] . Molecular weight of lysins is generally between 25-40 KDa , attack gram positive bacteria and composed of two genes: PlyCA and PlyCB [22].

Lysins by digestion of peptidoglycan produce a pore in cell wall [23], in the other hand high pressure in cytoplasmic cell cause burst bacterial cell. Lysins accelerate in cytoplasm during and cause burs cell in late stage of lytic cycle [24]. Lysins need a protein so called Holin to reaches their substrate [25]. Holin produce pore in inner membrane cell leading to access lysins to peptidoglycans [26], (Fig. 2).

History of phage therapy

Phages can use as a synergetic with antibiotic or alone to reduce human infection, nowadays phages use to control of MRSA, campylobacter, Listeria, pseudomonas, vibrio cholera and shigella [27, 28].

Phage eliminated from the body in the absence of the host bacterial cell [29], and don't effects the microbiota [30]. There are two type of infection: one pathogen and mixed pathogens. In mixed pathogen two ways can be selected: 1) use widespread phage or 2) mixed (cocktail) phages [31].Many studies have been shown efficacy using from phage therapy (Table 2)

Phage display

Phage display can use for detection of various biological structure including cell peptide, peptide

TABLE 1. Comparison phage therapy and antibiotic therapy with each other.

Antibiotic	Phage	Reference
Drug resistance	Without resistance / mutation to effect bacterial cell	**[7]**
Collateral damage	Specific to host	[8, 9]
-	Different mechanism from antibiotic	[10]
-	No immune response	[11, 12]
Multidrug resistance	Control multidrug resistance	[13]

Narrow host range is the most basic problem in phage therapy [14], to solved this problem can used mix phage so called cocktail [14] that is more effective than one phage. This event because of synergism effect between all phages that are inside of cocktail [15].

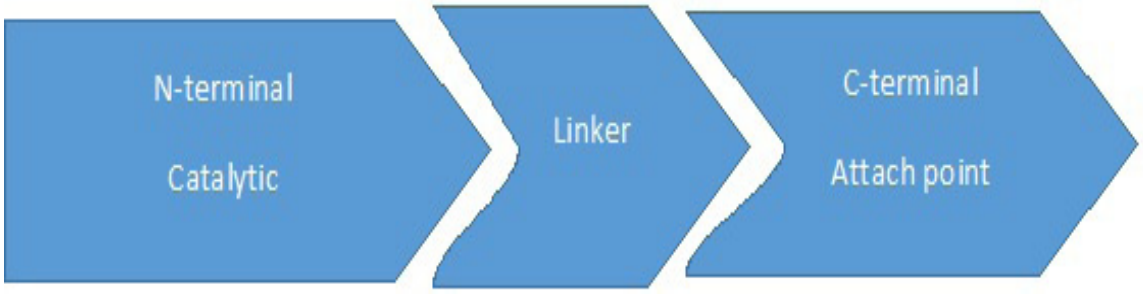

Fig. 1. Structure of phage lysins. C-terminal attaches to the cell wall carbohydrate and N-terminal causes lytic activity.

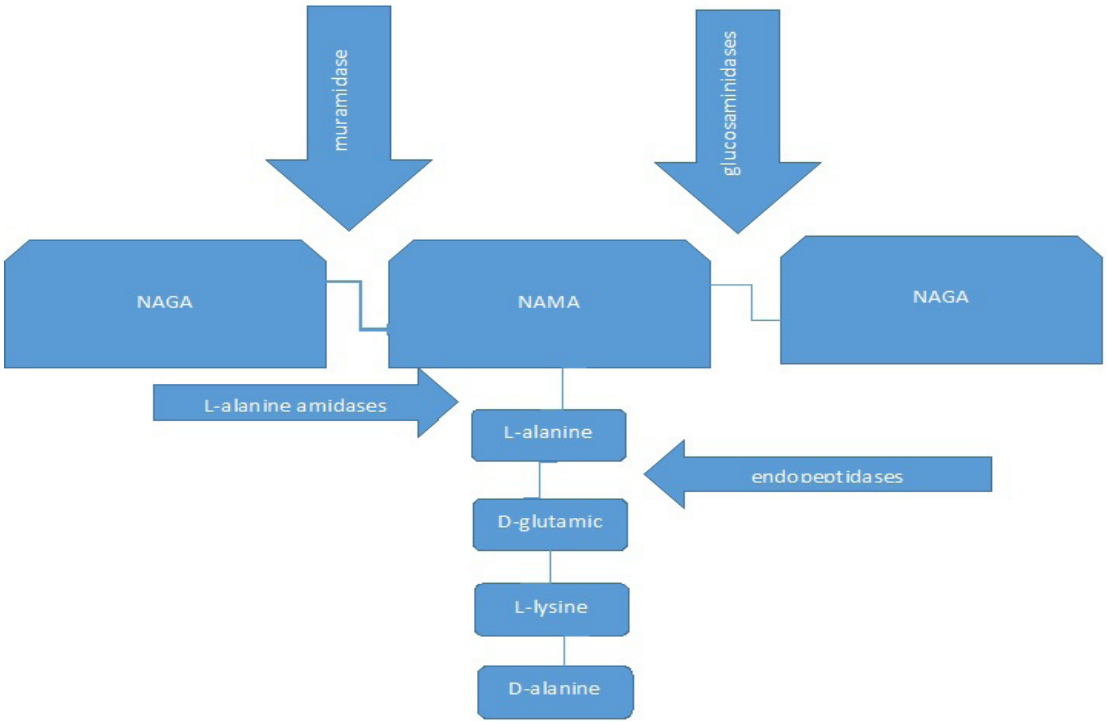

Fig.2. Lysins have four cleavage sites: 1) muramidase: that cleaves bond in N-acetylmuramidase, 2) glucosaminidases, 3) L-alanine amidase that cleavage bond between sugar (NAMA) and alanine and 4) cleavage bond between interpeptide bridges [26].

TABLE 2. Some studies was done about phage therapy.

Author	Title	Year	Conclusion	Reference
Marion Dalmasso et al.	Human Gut Show Promising Potential for Phage Therapy	2016	Three coliphage isolated from feces and was used in combination, data shown the phages inhibited the E.coli grows, in next step combination of phage with ciprofloxacin reduced the E.coli grows.	[32]
Cha sb et al.	Effect of bacteriophage in enterotoxigenic Escherichia coli (ETEC) infected pigs	2012	Used lytic phage cj12 as a bio-control, after 1 week of feeding phage pigs were challenged with ETEC. Result shown that in 10^8 CFU pigs are more resistance to diarrhea.	[33]
Leron Khalifa et al.	Targeting Enterococcus faecalis Biofilms with Phage Therapy	2015	They Isolated phage from sewage against Enterococcus faecalis and shown that this phage can destroy E.faecalis. This phage has a efficacy on biofilm.	[34]
Mark Fenton et al.	Recombinant bacteriophage lysins as antibacterials	2010	Reviewed the effects of lysins in control of bacterial infection. They conclude that the recombinant lysins can use as an antibiotic agent or with antibiotic as a synergism to destroy pathogen bacteria.	[35]
S. P. Goff et al.	Phage Therapy: a Step Forward in the Treatment of Pseudomonas aeruginosa Infections	2015	Reviewed the history of phage therapy against p.aeruginosa and shown that the phages are powerful tools against P.aeroginosa.	[36]

mediated drug delivery system [37] natural and biological polymers, ions, inorganic materials and identify cellular target [38]. Phage display widely used to screen peptides, antibodies and proteins with the advantages of high efficiency, simplicity and low cost [39]. phage can be collected from surface a wide variety of peptides and proteins [40] . The selection procedure allows separating of phage binders and using inexpensive technology to purify the phage. In the other hand phage display can used to produce monoclonal antibody against disease[41]. George P. Smith in 1985 showed to fusing the peptide of interest to gene III of filamentous phage[42]. Recently, the phage display technique has been used in an attempt to preparations of antivenom [43]. . Phage display allowed the ability to connect genetic information with protein function for a large number of protein variants together [44].

Many antigens are carbohydrates and can be screened and identified by phage-displayed random peptide libraries, these isolated peptide coupled with carrier proteins can be used as vaccine candidates to stimulate stronger antibody responses [45-47]. Vaccination with a combination of phage-displayed peptides from (heat shock protein) [48] *Candida albicans* elicited specific antigen cytotoxic T cell respond. More advanced therapeutic effect of the phage emerge when it is modified to express a targeting component specific for the treatment of cancer, infectious diseases and autoimmunity [49]. Filamentous phage M13 that loaded with chemotherapy medicine like Doxorubicin and displaying a targeting peptide killed cancer cells and can used as drug delivery [50].

Phage represents an important approach to producing peptides and other agent therapeutics. Transfer DNA gene using randomly and molecular biology techniques to phage, can be displayed on the phage surface and can be great diverse peptide libraries. The phage library can be incubated with a target structure and the phage which connects can be separated and sequenced to detect the Primary structure. The phage display process, whilst define a lot of methods and it has been used to drug-development process, contain the capacity for the phage particle itself to be used as a drug carrier targeted to a particular cell type or pathogen in the body [51], (Fig. 3).

Conclusion

Recently the methods of Phage display and therapy are more effective in treatment, detection and less expensive than other therapies ways, because the phages are kind of virus can mutate

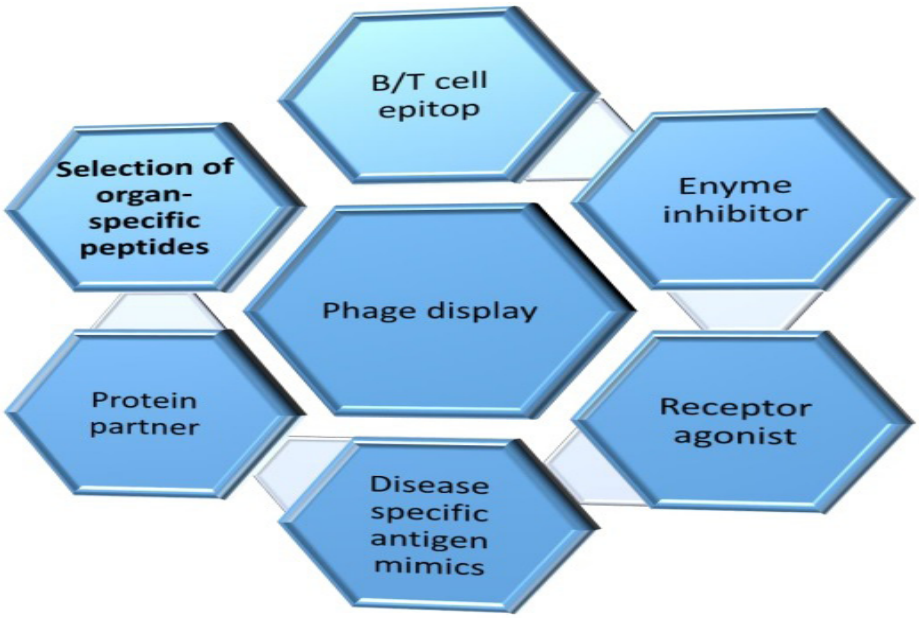

Fig. 3. Application of phage display in detection of biological structure [51].

himself to effect mutate bacterial cell that different from wild type. Treatment of many diseases are crucial problem in modern life, because often traditional treatment due to failure. Phage can duplicate himself in infection site and after reduction of host bacterial cell phage dose also reduced. Phage in millions of years adopt himself with bacterial cell and change and modified his receptor to identification bacterial ligand, in the other word phage cannot attach to eukaryotic cell and obviously cannot damage human cell and no immune reaction was seen. In addition with display and detect we can achieve new agent or drugs for treatment of difficult to cure disease.

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Conflict of interest

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