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Peptide Phage Display Technology Advancement and Uses in Biomedicine

Khushboo Panwar, Satyabrat Dutta*, Richa Sarkar, Esha Sinha, Ambika Arun, Gorre Venu, Arpita Sain and Sudhir Kumar Prajapati

Indian Veterinary Research Institute, Bareilly, Izzatnagar, Uttar Pradesh-243122, India

**Corresponding author*

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A B S T R A C T

A potent research tool for high-throughput protein interaction screening is a combinatorial phage library. Phage display has established itself as the most widely used molecular display technology. It is possible to find peptides that can bind target molecules and control their function by screening phage- displayed random peptide libraries. B-cell and T-cell epitope mapping, selecting bioactive peptides bound to receptors or proteins, disease-specific antigen mimics, peptides bound to non-protein targets, cell- or organ-specific peptides, and developing peptide-mediated drug delivery systems are all possible uses for phage-displayed peptide libraries. For fundamental science and translational medicine, employing peptides as targets that have been discovered through phage display technology may be helpful. The most recent developments in the use of phage-displayed peptide libraries for applied biomedical sciences are outlined in this review article.

Introduction

A peptide or protein is fused with a bacteriophage coat protein and exhibited on the surface of a virion in the selection method known as "phage display." George P. Smith first introduced this technology in 1985 when he showed how to display peptides on filamentous phage by fusing the desired peptide to gene III of the phage (1). Random peptide libraries that are displayed on phages allow for functional access to the peptides and create a physical connection between the genotype-the DNA that encodes the peptide-and the phenotype.

These libraries are well suited for screening procedures in which binding clones are distinguished from nonbinding clones by affinity purification.

Affinity selection allows for the identification of peptides that bind to specific targets (called biopanning). In order to perform biopanning, an immobilized target is incubated with a display library before non-reacting phages are thoroughly washed away. Binders are often amplified in the proper host cells after being eluted with acid or high salt. Targets that bind with high affinity are often

found after three to five rounds of biopanning. The DNA of each unique clone can then be sequenced to establish the peptide's basic structure. This method makes it simple to find peptides that bind target molecules in a particular way.

The development of peptide-mediated drug delivery systems, B-cell and T-cell epitope mapping, the selection of bioactive peptides bound to receptors or proteins, the selection of disease-specific antigen mimics, the selection of peptides bound to non-protein targets, the selection of cell- and organ-specific peptides, and other applications are all possible with the help of peptide-displayed peptide libraries. It may be possible to use targeting peptides discovered using phage-displayed peptide libraries in basic science and translational medicine. In this review paper, we go through each of the biomedical sciences' phage-displayed technology platform applications in depth.

Epitope mapping

The creation of antibodies targeted toward foreign protein epitopes is triggered by the presence of antigen, which stimulates host humoral immunity. Understanding the etiology of pathogen infections and creating efficient diagnostic tools, therapeutic antibodies, and vaccinations all depend on having knowledge of these protein epitopes. Immune system elements such as antibodies, B cells, and T cells identify an epitope (also referred to as an antigenic determinant). Antigens' epitopes can either be linear or conformational, depending on their structural characteristics (2).

Antigens containing some continuous amino acid sequences have linear epitopes, and these sequences match the antigens' fundamental structures. Contrarily, conformational epitopes, which are based on the tertiary structure of the protein, comprise discontinuous amino acid sequences of antigens. Several experimental techniques, including Pepscan (3), co-crystallization (4), nuclear magnetic resonance (NMR) (5), computational docking (6), and site-directed mutagenesis (7), can be used to find B-cell epitopes. The phage display method offers a quick and affordable way of mapping B-cell epitopes (8–10). Previous research has used a variety of phage-displayed random peptide libraries to find B-cell epitopes (11–15) or neutralize monoclonal antibody epitopes (mAbs). (11, 14, 16).

Polyclonal antibodies, like patient-specific sera or immunized mouse antibodies, can also be collected on solid discs or magnetic beads and then reacted with a large library of random peptides, in addition to mAbs. By biopanning with antibodies from complicated sera of patients with a variety of illnesses, including severe acute respiratory syndrome (SARS) (17), infection with the human papillomavirus (HPV) (18), and infection with avian influenza viruses (AIV) (19), peptides have been chosen. Certain peptide-based antigens are beneficial for serological diagnosis, and some are suitable for the production of vaccines, based on information about B-cell epitopes from polyclonal antibodies (17, 20, 21). The chosen disease- specific epitopes may be extremely helpful in determining the causative agent (17).

Disease-specific antigen mimics selection

Phage display peptide libraries have a lot of potential because they can find some peptide compounds that imitate epitopes (named mimotopes). Although mimotopes always exhibit discontinuous sequences and have fewer matches to the primary amino acids of antigens, they can still cause an antibody response that is identical to or very comparable to that of the native epitope.

For the creation of diagnostic or preventive reagents, serum or cerebrospinal fluid samples from patients with viral infections (22, 23), rheumatoid arthritis (24), multiple sclerosis (25), autoimmune thrombocytopenic purpura (26, 27), and neurocysticercosis (28) must be screened for disease-specific epitopes/mimotopes in phage-displayed peptide libraries. Peptides have been chosen by biopanning serum samples from HPV (18), SARS (17), and AIV (19) infected patients.

Broad-spectrum antibodies against the avian H5N1 influenza virus are amenable to mimotope-based detection (29), and it has been demonstrated to enhance serological detection of SARS (17) and rheumatoid arthritis (30). Another illustration is the recently discovered peptides that bind to cholera toxin. Acute diarrhea would arise from the cholera toxin, which is released by *Vibrio cholerae* and can penetrate host cells by binding to GM1, a monosialoganglioside. Cholera toxin B (CTB) subunit biopanning could be used to find CTB-binding peptides that structurally resemble GM1 and act as new inhibitors of CTB binding on epithelial cells, preventing the physiological effects of cholera toxin (31).

Additionally, mimotopes can be utilized to describe unidentified beginning events and offer gives an idea about the pathophysiology of diseases. An immunopositive peptide with a high degree of resemblance to autoantigens, such as heterogeneous ribonucleoproteins (hnRNP), cytochrome c, fibrillarin, and late protein UL94 of human cytomegalovirus (CMV), was screened by biopanning with antibodies from systemic sclerosis patients (32).

Systemic sclerosis patients' sera included immunopositive peptide-based affinity-purified antibodies that interacted with an endothelial cell surface component and caused apoptosis. AEG-1, a human protein on human endothelial cells, is cross-reactive with a dengue anti-NS1 antibody B-cell epitope and may contribute to hemorrhagic fever (DHF) or dengue shock syndrome (DSS) in some dengue patients (33).

Recently, serum antibodies from prostate cancer patients were shown to have an antigen peptide that mimicked the alpha-2-Heremans-Schmid glycoprotein, also known as fetuin-A (34). Researchers showed high serum reactivity in a sizable cohort of patients with metastatic prostate cancer and enhanced serum antibody reactivity to fetuin-A with disease progression in the index patient using this antigen mimic peptide (34).

Choice of bioactive peptides linked to proteins or receptors

For different receptors

Membrane receptors are crucial for electrical and biochemical transmission between cells in vital physiological processes. As a result, pharmaceutical businesses frequently concentrate on creating medications that target membrane receptors (35, 36). Utilizing phage- displayed random peptide libraries, novel receptor ligands were found that might either be agonists or antagonists (37–40). Peptides that target the thrombopoietin receptor (TpoR) and the erythropoietin receptor (EpoR) are two common examples of agonist peptides chosen via phage display (37, 38). The extracellular domain of EpoR undergoes conformational changes following Epo mimetic peptide treatment, which result in intracellular signal transmission (37). This finding might serve as the foundation for creating small-molecule Epo mimics. On the other hand, the TpoR-targeting short peptides can engage in binding competition with thrombopoietin, the receptor's endogenous ligand, and promote the growth of a TPO- responsive cell line (38). Additionally, phage display-derived membrane receptor antagonists have been discovered (41–43). For instance, vascular endothelial growth factor (VEGF) binding to the kinase domain receptor (KDR/FLK1 or VEGFR2) plays a significant role in angiogenesis. By using phage display, peptide antagonists that stop VEGF-mediated angiogenesis have been produced (43, 44). A chemoattractant called human CXC ligand 8 (hCXCL8) interacts with the inflammatory receptors hCXCR1 and hCXCR2. The development of new medicines for the treatment of inflammatory illnesses has been based on research into the inhibition of hCXCL8 binding to hCXCR1 and hCXCR2 by antagonistic peptides (45-47).

For inhibitors of enzymes

The production of aberrant enzymes has a role in the development of several diseases, making them suitable targets for the creation of new medications

that block the activity of these enzymes. The peptide substrate inhibitors that modify enzyme activity have been found via phage display (48, 49). It has been used to locate substrates and produce protease inhibitors since filamentous phages are resistant to a variety of proteases (50). Bahudhanapati *et al.,* identified selective inhibitors of collagenase-1 (metalloproteinase 1, MMP-1) by screening variants of tissue inhibitors of metalloproteinases-2 (TIMP-2) using phage display. TIMP-2 is a broad-range inhibitor of matrix metalloproteinases (MMPs) (51). In addition to protease inhibitors, phage- displayed random peptide libraries have also been used to find peptide-based inhibitors fora number of other enzymes, including human HMG-CoA reductase (52), ubiquitin ligases(53), and tyrosinase (54).

Protein-protein interactions

Protein-protein interactions control the mechanisms of a number of critical regular physiological operations in cells and tissue. A powerful and adaptable technique for examining protein-protein interaction is phage display (55–58). It can be used to map intracellular connections of the specific protein domain and is applicable to a variety of protein interaction partners and applications. Src homology (SH) 3 domains, which are highly conserved protein interaction modules made up of 50 to 70 amino acids, are excellent examples of protein interaction partners. Several proteins with unrelated functions also contain SH3 domains. All human SH3 domains are expressed on the surface of M13 bacteriophage thanks to a library created by Kärkkäinen *et al.,* (59); this allows for the investigation of human SH3 domain binding to target proteins like human immunodeficiency virus-1 Nef, p21-activated kinase (PAK)2, and ADAM15. Similar libraries were also created by Voss *et al.,* to define the SH3 domain that interacts with the intracellular portion of the Fas ligand. The scientists also discovered a number of new SH3 domains that may also be connected to FasL (60), in addition to the recognized SH3 domains (61, 62). In general, carbohydrates make up a lot of tumor antigens. By using phage-displayed random peptide libraries, it is possible to screen for and identify epitopes that imitate low immunogenic polysaccharides or carbohydrate antigens (63, 64). To promote greater antibody responses, these isolated peptide mimotopes in combination with carrier proteins may be employed as vaccine candidates (65, 66).

By screening random peptide libraries, the phage display method has also enabled us to discover new peptides directed toward RNA of interest (67, 68). It is possible to prevent cell-free translation by using specific peptides that target helix 31 of bacterial 16S RNA (67). Bose *et al.,* discovered a selective peptide that binds to pre-miR-21 using phage display, blocking Dicer processing and decreasing miR-21 expression (69, 70-72). In order to monitor the environment in soil and water, Liu *et al.,* recently used a phage display to identify peptide ligands that recognized the insecticide imidacloprid (73). Selecting certain peptides for use against nanomaterials can be accomplished via the phage display biopanning approach. These peptides that bind to nanomaterials and are exhibited by phage are widely used in the field of nanotechnology (74-79). In order to functionalize the surface of conductive polymers and enable diverse electronic and biological applications, peptides from phage-displayed libraries can be precisely attached to a conducting polymer (80). Additionally, the combinatorial phage display peptide library was used to acquire the Au-, Ag-, Ti-, Pt-, and Pd-binding peptides (81- 84). For usage in nano- and biotechnology, notably in the realm of molecular biomimetics, such metal, and semiconductor-targeting peptides have been genetically produced (84).

Peptides selected specifically for cells

A high-throughput method for finding peptides that specifically bind to one cell type is peptide phage display by whole-cell panning. The use of peptide-displayed phage to discover peptide binding to various cell types was first described by Johnston and colleagues (85). The procedure of "biopanning," in which the binding affinities of the targeted phage

clones are enriched, is the most popular screening technique. It can be carried out in vitro on a variety of cell types, including processed cells, cultured cell lines, primary cells derived from human patients or animal models, and (fixed cells, activated cells, etc.). In vitro biopanning of phage- displayed peptide libraries using different cancer cell types has been the subject of multiple investigations over the past ten years (86–90) in an effort to find cell-specific ligands. Selection can be carried out on either adherent or fixed cells, depending on the ligand's uses. The experimental strategy can be changed to isolate phages, which attach to peptides or cell surfaces and cause the cellular uptake of the peptides. Cells are treated with peptide-displayed phage libraries for a predetermined phase of time. The cells are then rinsed to eliminate weakly attached and non-specific phages. Blocking chemicals like BSA (Bovine serum albumin) are occasionally employed to lessen the peptide or phage's cross-reactivity. To acquire phage clones with strong binding to the chosen target and eliminate non-specific binding from the background, an unattached phage must be removed. Using a variety of elution techniques, including the use of acidic buffers, dithiothreitol, and high ionic strength, which tend to decrease the interaction between the peptide and the target, the phage attached to the target is retrieved. These elution processes, however, may only partially disrupt peptide-target contacts in the case of strong peptide-target interactions, leading to the loss of the high-affinity phage clones (92).

There are various benefits to using whole cells as the target for in vitro biopanning rather than isolated proteins. The cellular receptors expressed on living cells can maintain their natural states, including their biological activities and functions (correct protein folding, quaternary structure, expression level, and connection with nearby proteins). The isolation of peptides that mediate particular biological functions can be accomplished through biopanning using customized techniques. For instance, selection might be used to target internalized or surface-bound peptides. Surface-bound phage can be isolated by phage direction elution. Phages with internalizing properties can be identified if surface-bound phages are eliminated using low-pH washes or by being subjected to protease treatment. Additionally, the identification of cell surface molecules with unidentified biological activities is made possible by the use of whole cells for biopanning. This can be used to describe cell surface proteins and offer details on molecular differences between healthy and diseased cells (such as expression level and protein localization) (91-93). The extraction and affinity purification of membrane protein, followed by the mass spectrometric identification of the purified protein, are the main steps in conventional receptor identification. The difficulties with this strategy, however, stem from the inability to preserve the natural connection between the targeted peptide and the separated entire membrane receptor (89, 94).

Peptide-mediated drug delivery system development

Physical transport barriers within tumors hinder the delivery of anti-cancer medications to solid tumors, and these limitations directly affect the therapeutic index. In animal models, drug delivery systems with fine spatiotemporal control have shown promise in improving medication delivery. There are many nanoparticle delivery methods for anticancer medications in use today, and it has been demonstrated that these systems have anticancer benefits by enhancing the pharmacokinetic and pharmacodynamic characteristics of the pharmaceuticals they are used with (109). The most sophisticated type of particulate drug carrier is liposomes. Targeting liposomes, which are made by joining specific ligands to liposomal medicines, can be used to deliver medications with molecular targets. Advances in liposomal systems have made it possible to build targeted liposomes. The three primary components of peptide- mediated liposomes are liposome carriers and targeting ligands. Weak bases like doxorubicin or vinorelbine can be efficiently encapsulated into liposomes using remote loading techniques like the ammonium sulfate approach (110) and the pH gradient method (111,

89). Schedule- dependent medications, such as topotecan and vinca alkaloids, make logical candidates for liposomal administration due to their efficiency in lengthening the duration that cancer cells are exposed to therapeutic drug levels. By using peptide-mediated liposomes, it is also possible to avoid damaging side effects and the exposure of healthy tissue to cytotoxic medications. Effective medication administration is hindered by high tumor interstitial fluid pressure (IFP) (112, 113). Increased IFP correlates to decreased transcapillary transport in malignancies, which limits the uptake of medicines. This method avoids the issue of high tumor IFP (89, 113, 114) and enhances treatment efficacy, thereby lowering inadequate tumor response, quick disease relapse, and development of drug resistance due to insufficient dosages, which are frequently observed when employing standard chemotherapies.

In comparison to bigger biomolecules like antibodies, the use of peptides as targeting ligands has a number of benefits, including ease of synthesis, structural simplicity, low cost, low immunogenicity, small size, ready diffusion, and simple targeted formulation assembly. Previous research indicated that the clearance of antibody-modified nanoparticles from circulation may be increased by utilizing bigger biomolecules as targeted ligands (115–117). This might be caused by the RES's non-specific binding to and absorption of nanoparticles (116). Targeting moieties may boost drug accumulation in tumor tissues, according to earlier research using various targeted delivery systems (118, 119). When compared to non-targeted medications, targeted nanoparticles have not always resulted in a measurable rise in overall tumor accumulation. Transferrin (121) and antibodies (120) are examples of macromolecule- targeting ligands whose effects on tumor accumulation and biodistribution are insignificant (122-124).

Results and Discussion

Combinatorial phage-displayed random peptide libraries are excellent resources for examining how peptides interact with other substances (or materials). The identification of B/T cell epitopes (11–19), disease-specific antigen mimics (22–34), receptor agonists/antagonists (35–45), enzyme inhibitors (48–54), and protein partners (55–62) have previously been the subject of research. A number of scientists have recently used this method to study new fields, including chemistry (70–72) and materials science (74–84). Phage display has various drawbacks despite being an effective technology. The number of phage-displayed amino acid residues, the use of appropriate selection conditions, the stability and quality of the phage display libraries, and adhering to the proper screening protocols are all critical considerations that may affect the quality and desirability of the ligand peptides produced. Functional target peptides are more likely to be obtained if these crucial criteria can be defined. Additionally, combining peptide data from phage display with bioinformatics tools may enhance peptide quality. The introduction of genetically encoded non-natural amino acids into phage-displayed libraries by Tian *et al.*, (125) and Sandman *et al.*, (126) opened the door for more chemical diversity in this field. A new phage-displayed hybrid method and synthetic chemistry were also integrated by Woiwode *et al.*, (127).

It's common knowledge that cancer cells frequently overexpress particular antigens in comparison to normal cells. Molecules that can identify these tumor antigens with high specificity make good candidates for use as potential agents in cancer chemotherapy that direct treatment to specific tumor locations. The field of cancer therapy has been significantly impacted by therapeutic monoclonal antibodies, antibody-drug conjugates (ADCs), peptide- drug conjugates (PDCs), and peptide-mediated drug delivery systems. The therapeutic efficacy of antibodies acting directly by blocking receptors or acting as agonists may be restricted. The effectiveness of antibodies has been shown to be significantly influenced by antibody- dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) (128, 129). Unfortunately, immune suppression, immunological

escape, complement inhibition, and other factors can prevent anti-body therapy for patients with malignant tumors from having a therapeutic effect. ADCs provide a potential solution to this problem by increasing cytotoxicity to cancer cells and so minimizing undesirable side effects. ADCs are already recognized as effective anticancer treatments, but there are still a number of drawbacks to this class of medicines, including tumor penetration, high manufacturing costs, and difficult conjugation chemistry (130). For the synthesis of PDCs for cancer therapy, a number of peptides, including RGD motif peptides (131-136), cell-penetrating peptides (137-141), and tumor cell-specific peptides (142-145), are employed. However, is a significant disadvantage PDCs have poor pharmacokinetics and a short half-life in circulation due to their high proteolytic instability restricts their therapeutic applications (146).

Increased drug accumulation at the target tumor site is possible with drug delivery using antibodies or ligands that bind to specific receptor molecules on tumor target cells; however, the actual percentage of drugs accumulated at the tumor site was frequently only a few percent of the total dose administered. Active targeting might be more effective if an efficient ligand- receptor interaction is discovered. Although there is still more work to be done in the area of targeted medicine delivery, this could change within the next few years. It is anticipated that more targeted medication delivery nanoparticles would eventually receive FDA approval.

Although new cancer medications are constantly being developed, the majority of these medications only have modest effectiveness in combating cancer and have a less-than- ideal ability to extend the lives of cancer patients. Small molecule medications benefit from greater tissue penetration capabilities but lack tumor-specificity and have a short half-life. Protein medicines have a high tumor specificity, but because of their greater molecular sizes, they are less able to penetrate tumors. Peptide-mediated drug delivery systems maximize the advantages of the two therapy regimens while minimizing their drawbacks by combining highly selective peptides with powerful small-molecule medicines. A drug delivery system should be very clinically effective while minimizing side effects. By reducing drug distribution to non-target tissues and enhancing drug delivery to the target tissue. Next-generation targeted agents, such as peptide-mediated targeting liposomes, can be created by combining peptides with a variety of liposomal medications thanks to the targeting liposome technology's modular structure. But as of now, neither peptide-drug conjugates nor peptide-modified nanoparticles have been commercially viable. Before peptides can be widely used as targeting molecules, however, a number of obstacles must be cleared. These include creating the proper ligand for the targeted receptor, comprehending the mechanisms of ligand-receptor uptake, disposition, trafficking, and recycling, and adhering to Chemistry, Manufacturing, and Control (CMC) regulations.

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