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№ 2769

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February 26, 2020

3rd National Conference on Green Technology and Science for Sustainable Development
© 2020 IJSRST | Volume 5 | Issue 5 | Print ISSN: 2395-6011 | Online ISSN: 2395-602X
International Journal of Scientific Research in Science and Technology

Engineering Protein Nanocages as Carriers for Biomedical Applications

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ABSTRACT

Protein nanocages have been explored as potential carriers in biomedicine. The application of protein-based nano particles has increases rapidly in drug delivery, vaccine development, and biocatalysis. It formed by the self-assembly of protein subunits. The caged structure has three surfaces the interior, the exterior and the intersubunit. Therapeutic and diagnostic molecules are placed in the interior of nanocages, and the external surfaces improve their biocompatibility and targeting abilities. There are some modifications in the intersubunit interactions to modulate the self-assembly profile with implications for tuning the molecular release. Protein nanocages have been modified using chemical & genetic engineering techniques to impart non-natural functions that are responsive to the complex cellular microenvironment while delivering molecular cargos with improved efficiencies and minimal toxicity.

Keywords: Nanocages, Protein-based nanoparticles, Vaccine nanocage, Biomedicine, Biocatalysis, virus-likepartical.

I. INTRODUCTION

Protein nanocages have been explored as potential carriers in biomedicine. It formed by the self assembly of protein subunits. The caged structure has three surfaces the interior, the exterior & the intersubunit.[1] The minimum ability to targeting and improper bio distribution are major flaws in current drug-based therapies that resist reaching high local concentrations of the therapeutic agent. Such weaknesses impose the administration of high drug doses & cause t have undesired side effects, limited efficacy and enhanced production costs. To fill this gap, health-focused nanotechnologies have put under screening a growing spectrum of materials as potential components of nanocages, whose properties can be tuned during fabrication.[2]

Protein engineering is the study to make nanocages protein structurally more stable and functionally more modified & active.

Bio-engineers have start to utilize the advantages of nanocages by changing their structures. All approaches have been developed to construct nanoreactors for biocatalysis and synthetic biology. These artificial specialized structures provide a new platform to design a generation of nano technique for synthetic biology.[4]

Advances in the fabrication and design of carriers such as cationic liposomes, micelles, block copolymers, carbon nanotubes,

dendrimers and inorganic nanoparticles are restricted by severe toxicity and low delivery efficiency. Nanocarriers are potential alternatives to synthetic ones they satisfy most of the key features, like biocompatibility, water solubility and high cellular uptake efficiency with minimal toxicity. Examples of nanocarriers include protein nanocages such as viruses, ferritin and many others that are formed by the self-assembly of protein subunits which resulting in a cage-like structure. Monodispersed subunits are modifiable by chemical and genetic methods.[1]

Protein engineering and directed evolution are powerful technologies for enquiry of protein sequence function relationships. These methods have been used to build both plant-derived proteins and exogenous proteins expressed in plants. Self-assembling proteins which create diverse architectures are widely used in material science and nano biotechnology. One type is belongs to protein nano cages, which are compartments with nano sized internal spaces. Because of the precise nanoscale structures, proteinaceous compartments are ideal materials for use as general platforms to create distinct microenvironments within confined cellular environments.[4] Protein engineering is the process by which a researcher modifies a protein through substitution, insertion, or deletion of nucleotides in the encoding gene & with the goal of obtaining a modified protein that is more suitable for a particular application or purpose than the unmodified protein.[3]

Protein engineering plays an important role in medical research, such as in drug discovery & diagnostics, because of the relation between proteins, genes and diseases . Understanding the protein functions help to understand diseases, most of current drugs are either proteins or they target specific proteins in the body. Identifying unique protein property associated with specific diseases is a very important and promising area in the field of clinical protein engineering.[5]

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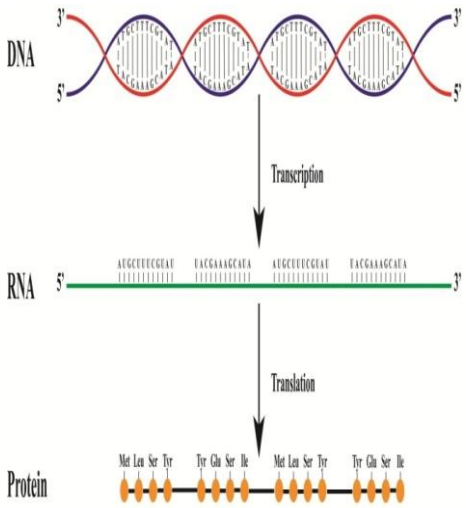

Fig. 1.1 formation of protein

Protein is generally made by the DNA & RNA. DNA send message of requirement to messenger RNA by transcription and RNA translate the message to form protein. By change in structure of genes the structure of protein can be change.

II. APPLICATIONS

1. Vaccine Development

Natural and synthetic Protein nanocages have potential use in biomedicine as vaccines and as DDSs. While modifications on the outside of Protein nanocages have been shown to be aviable strategy for vaccine development, the encapsulation of target molecules inside Protein nanocages remains a more challenging option. For example, VLPs have been successfully developed and introduced as vaccines. In these VLPs, which lack genetic material, the outer surface is chemically or genetically modified to introduce a large number of anchoring points to which antigens can be connected to increase their immunogenicity. In another example, HBc particles, which have the ability to serve as carriers of foreign B cell and cytotoxic T lymphocytes epitopes, have been used to genetically display antigens for malaria, tuberculosis, human papillomavirus (HPV) 16 cytotoxic T lymphocytes epitope E7, and dengue virus type.

2. Drug Delivery Systems

Drug delivery systems aim to minimize these limitations by altering a drug's solubility, pharmacokinetics, and biodistribution. Emerging nanotechnologies, in particular, NPs, show great promise as DDSs for cancer treatment. Yet, very few synthetic NPs have advanced to become approved clinical therapies. This is due to their significant limitations, which include physicochemical heterogeneity, problematic functionalization, instability in physiological solutions, poor tumor penetration, and toxicity in biological systems. The use of Protein nanocages as nanocarriers is a promising alternative to synthetic NPs for the development of "smart" delivery systems. Protein nanocages can be designed and produced to trigger the release of their cargo in response to changes in pH, chemical stimuli, redox potential, and temperature.

3. SOME OTHER APPLICATION

- The application of nanostructured materials to solve biomedical problems has evolved into an active field of research known as nanomedicine.
- Production of neutralizing antibodies like HBV, HPV, influenza, HIV, hepatitis C virus, RSV, chlamydia infections and cancers such as cervical cancer and P815 tumors are a few diseases that have been targeted for vaccine development using the protein nanocage.
- It is anticipated that nanomedicine will bring in many opportunities for more effective diagnosis and treatment of diseases, eventually causing paradigm shifts to the pharmaceutical and biotechnological industry.

- In the context of cancer theranostics, therapeutic agents are increasingly integrated with nanostructures engineered with optimal size, shape and surface property to increase the solubility, prolong the blood circulation half-life, improve the pharmacokinetics and tumor targeting selectivity, and ultimately reduce the side effects.
- Understanding protein functions help to understand diseases, most current drugs are either proteins or they target specific proteins in the body.[5]
- In te pregnancy test the intense optical properties of gold nanocages are used as a chemically-stable, highly visible optical indicator.
- The use of gold nanocages in lateral flow assays for the detection of pathogenic toxins is a rapidly growing market.

III. METHODS

1 Identification

The identification of Protein nanocages has become easier due to the accessibility of genomic data and the development of powerful bio informatics software for genome mining. However, it should be noted that only a limited number of Protein nanocages have been studied in-depth, including nonviral Protein nanocages like ferritin, heat shock proteins (Hsp), DNA-binding proteins from starved cells (Dps), encapsulin, the E2 protein of pyruvate dehydrogenase, lumazine synthase, vault proteins, and virus-like particles (VLPs, which resemble viruses, but contain no viral genetic material andarethereforenon-infectious).

2 Production

Protein-based nanoparticles have been produced either in their natural hosts, as recombinant proteins in expression systems like bacteria, yeast, plants, and insect or mammalian cells or by cell-free protein synthesis. Selecting the most suitable production method can make a significant difference when it comes to achieving high production yields for protein nanocages. The self-assembly of nanostructures in cells depends on specific protein interactions.

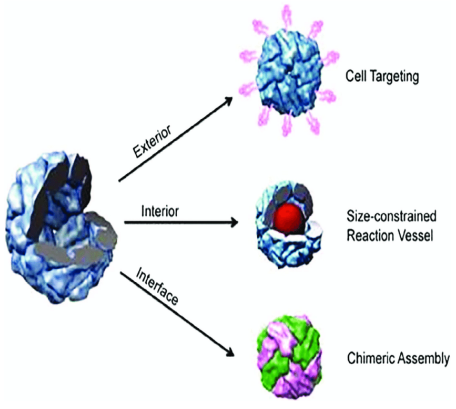

Fig.3.1 Protein cage modifications at distinct interfaces

3 Purification

Due to their large macromolecular structures, protein nanocages purification protocols tend to involve size exclusion chromatography (SEC) and differential centrifugation (e.g., sucrose gradient) steps. To achieve higher protein nanocages purity, SEC is generally combined with affinity chromatography, in which the protein nano cages displays a pre-selected purification tag (e.g.,histidine-tag),or ion-exchange, in which the outer surface charge of the protein nano cages is exploited.

4 Release behavior

One of the key requirements of drug delivery systems is the effective loading and release of drugs from the nanoparticle carriers. The strategies used to choose a delivery system is based on the system's structure and functions & the nature of the drug carried. Protein-based carriers and drugs could be chemically change by post-translational attachment of drug molecules to reactive side chains of amino acids such as amines, carboxyls, sulfhydryls and hydroxyls, as well as non-side chains through click chemistry.

IV. ADVANTAGES:

- The spacail control of functional groups displayed at well-defined locations through genetic or chemical modifications.
- Certain essential factors are good enough include drug efficacy, the target physiological environment, stability, safety, loading capacity and drug release kinetics of the carrier.
- It have ability to decorate the nanocarriers with multiple functional elements precisely and uniformly.
- Rapid response and high sensitivity.

V. DIS-ADVANTAGES :

- The detailed mechanisms for the uptake of the protein nanocages and their intracellular fates are not fully understood.
- The efficiency of delivery to the intended intracellular compartment remains a challenge.
- Nano cages are substrate depended .

VI. LIMITATION :-

Similar to other nanoparticles, the application of protein nanocages in biomedicine involves several challenges:

(1) low specificity,

(2) lack of cell uptake efficiency,

(3) absence of endosomal escape mechanism,

(4) low tuneable release properties,

(5) limited circulation time,

(6) potential to trigger an immunological response and clinical applications of nanocages are limited because of the structures' poor stability and cell permeability. To overcome some of these challenges, the

engineering of protein nanocages is required to impart non-natural functions.

VII. CONCLUSION:-

The majority of efforts have been focused on using protein nanocages to deliver anticancer drugs, exploiting protein nanocages to modulate the immune response is an emerging area of research. For delivering immune modulating agents for application in cancer immuneotherapies or autoimmune disease treatments the protein nanocages are good candidates. Viruses have the born ability to condense and deliver nucleic acids by cell receptor interactions. After studying the structure and functions of the protein subunits in viruses that are responsible for packaging and releasing nucleic acids, novel gene delivery systems can be constructed.

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