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Engineered nanoparticles mimicking cell membranes for toxin neutralization☆

Ronnie H. Fang, Brian T. Luk, Che-Ming J. Hu *, Liangfang Zhang *

Department of NanoEngineering and Moores Cancer Center, University of California, San Diego, La Jolla, CA 92093, USA

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ABSTRACT

Protein toxins secreted from pathogenic bacteria and venomous animals rely on multiple mechanisms to overcome the cell membrane barrier to inflict their virulence effect. A promising therapeutic concept toward developing a broadly applicable anti-toxin platform is to administer cell membrane mimics as decoys to sequester these virulence factors. As such, lipid membrane-based nanoparticulates are an ideal candidate given their structural similarity to cellular membranes. This article reviews the virulence mechanisms employed by toxins at the cell membrane interface and highlights the application of cell-membrane mimicking nanoparticles as toxin decoys for systemic detoxification. In addition, the implication of particle/toxin nanocomplexes in the development of toxoid vaccines is discussed.

Contents

1. Introduction to antivirulence therapies

Toxins represent a ranged attack mechanism employed by a variety of organisms to help aid in their survival. The more potent ones can have a large and immediate impact on human wellbeing, causing irreparable damage and oftentimes death. Toxin-secreting organisms are highly prevalent in nature, and notable examples include bacteria, snakes,

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* Corresponding authors.
E-mail addresses: c4hu@ucsd.edu (C.-M.J. Hu), zhang@ucsd.edu (L. Zhang).

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and insects among many others [1]. In the case of bacterial infections, the role of toxins is to allow the pathogen to better colonize and survive within the hostile environment of a host [2]. Venomous eukaryotes employ toxins as defense mechanisms or to immobilize prey [3]. In total, these damaging molecules represent a major worldwide health problem that affects people regardless of socioeconomic status or geographic location [4,5]. They can even be mobilized as biological weaponry, with anthrax representing one of the more notable examples in recent history [6]. As such, the neutralization of toxins is of high importance, and a great deal of research has been focused on this subject.

Because of their damaging nature and the significant role that they can play in different pathogeneses, targeting toxins represents a rational means of treating afflictions on a causal level. For example, in the case of bacterial infections, which represent one of the most common causes of illnesses in the world, toxin neutralization serves to disarm the pathogens and remove the agents directly responsible for many of the worst symptoms [7,8]. Due to the role of toxins in allowing pathogens to subvert immune defenses or obtain nutrients from nearby cells, detoxification also makes effective colonization of human hosts more difficult [9]. Further, antivirulence treatment strategies are less susceptible to resistance development, making them attractive alternatives to current therapeutic modalities [10]. This is largely due to the fact that they do not act on individual bacteria, lessening the Darwinian selection process that drives antibiotic resistance. Search for such robust treatments is becoming ever more important due to the rise of many antibiotic resistant bacterial strains that is far outpacing the development of new drugs [11,12].

Conventional strategies for the neutralization of protein-based toxins have relied heavily on structure-specific platforms such as antibodies, which can be generated with high affinity against specific toxin species [13,14]. However, because many organisms secrete multiple types of damaging toxins [15,16], effective antivirulence treatment requires simultaneous administration of multiple formulations. Combined with the need to identify virulence species, clinical application of structure-specific antivirulence platforms can be difficult, thereby prompting the development of broadly applicable anti-toxin platforms.

Upon inspecting toxin mechanisms, it can be reasoned that cell membranes present the primary barrier that toxins need to overcome to inflict their virulence effect. Such mechanistic similarity offers the opportunity for developing broadly applicable anti-toxin formulations. Recent research efforts have demonstrated multi-toxin neutralization by employing nanoparticulates with lipid membrane interfacing [17,18]. These emerging platforms take advantage of the fact that, regardless of their individual modes of action, all toxins must at some point interact with the cell membrane (Fig. 1). Further, nanoparticles inherently have properties that can benefit detoxification applications, including long circulation and the potential for multivalent toxin interaction. In light of these recent developments and their therapeutic implication, the present article reviews the evolution of cell-membrane mimicking nanoparticles with specific emphasis on toxin-related studies. Firstly, different mechanisms through which protein toxins interact, disrupt, and overcome the cell membrane barrier are described to highlight the role of the cell membrane interface in toxin actions. This is followed by an overview of the development of cell-membrane mimicking nanostructures and their application in protein toxin research as well as in biodetoxification. Finally, the implication of utilizing toxin-neutralizing nanocomplexes in antivirulence vaccination is discussed.

2. Interactions between toxins and cell membranes

To inflict their virulence effect on host systems, all toxins must interact in one way or another with cell membranes. Most often, toxins bind specific receptors on the cell surface, allowing them to effectively carry out their function. Once they make contact, there are several means by which toxins act. They can directly manipulate the membrane and its associated functions, or they can traverse the membrane barrier and disrupt intracellular processes.

2.1. Binding of toxins to cell membranes

Most toxins display a certain level of specificity toward individual components of cell membranes [19,20]. They can target specific biomolecules on the membrane surface such as proteins and lipids or they can be attracted by nonspecific interactions. This membrane affinity enables the toxins to carry out their biological function. Toxins can act directly on the membrane by causing physical disturbances or they can affect intracellular process such as protein synthesis, and their ultimate function often dictates the type of membrane moiety that is targeted [21,22]. Further, toxin receptors can be present on some cells but not on others [23,24], allowing the toxins to impact specific physiological processes.

2.1.1. Membrane-bound proteins

Proteins located on the cell membrane surface represent a major class of targets utilized by toxins. The large diversity and uniqueness of surface proteins enable toxins to carry out a large variety of functions with high specificity. Surface proteins can be essential for the binding and structural maturation of toxins, as is the case with ADAM10, a sheddase that is conserved in many mammals and is the target of the pore-forming α-hemolysin produced by the gram-positive bacterium *Staphylococcus aureus* [25]. The ability of α-hemolysin to lyse erythrocytes is species dependent and highly correlated with expression of this protein receptor [25]. Transmembrane ion channels in the plasma membrane are common targets whose functions are directly affected by peptide toxins found in venoms [26]. Aerolysin, a pore-forming toxin secreted by the gram-negative bacterium *Aeromonas hydrophila*, targets extracellular proteins anchored by the lipid derivative glycophosphatidylinositol [27]. Binding to glypiated proteins enables toxins to more effectively oligomerize by localizing and concentrating individual monomers onto lipid rafts [28]. Other examples of membrane protein-binding toxins include anthrax toxin, which targets two different receptors on the cell surface [29], and phospholipases secreted by pathogens or in venom that, besides their affinity to their lipid-based

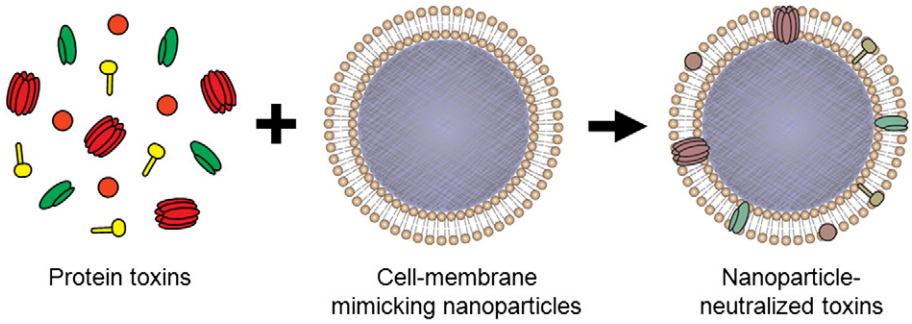

Fig. 1. Engineered nanoparticles for detoxification aim to mimic natural cellular membrane structures. By closely imitating natural cellular surfaces, such nanoparticles have the ability to bind protein toxins. These nanoparticles effectively divert toxins away from healthy cellular targets and allow for safe metabolism and elimination of the protein toxins.