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Microsurgeon *Hirudo medicinalis* as a Natural Bioshuttle for Spontaneous Mass Vaccination against Influenza A Virus

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ABSTRACT

Introduction: Recent report on existence of a stem region of hemagglutinin has arisen new hopes for vaccination of influenza A as it consist of a conserve fusion peptide shared across several influenza subtypes and can be targeted by human immune system. ***Methods:*** Given that traditional vaccination based on live attenuated viruses often fails to surpass such viral infection, a great deal of attention has been devoted to develop a safe yet efficient system for vaccination influenza A. We believe that a natural bioshuttle can be recruited for spontaneous mass vaccination. ***Results:*** Thus, here, we hypothesize that a bioengineered transgenic *Hirudo medicinalis* can be considered as an alive bioshuttle for in-situ vaccination against influenza A virus. By introducing the designated gene(s) encoding the target fragment (i.e., stem region of hemagglutinin), this microsurgeon can act as a rapid microproducer of viral proteins for in-house mass vaccination through imparting the necessary proteins such as those, naturally presented in leech's saliva. ***Conclusion:*** This peculiar bioshuttle can be easily exploited as a medical modality choice at home resulting in greater patient compliance.

Introduction

The current pandemic flu that originated in Mexico in April 2009, as a major cause of morbidity and mortality, resulted in 3–5 million cases of severe illnesses and 250,000–500,000 deaths worldwide (Chen and Subbarao 2009; Bhakdi *et al.* 2009). In 2003, the Advisory Committee on Immunization Practices (ACIP) has announced the effectiveness of the annual influenza vaccination in preventing influenza-related hospitalization and death (D'Heilly *et al.* 2004). Since the traditional vaccination modalities using live attenuated viruses appear to encounter many problems, the protein based vaccines hold great promise against world threatening diseases as a safer alternative that can be used easily (Murthy *et al.* 2003). There exists plethora of researches which prove activation of the immune response through influenza protein subunit as well as inactivated or attenuated virus. Likewise, lots of licensed protein-based vaccines are being developed that are able to activate the immune response against viruses' main surface proteins, so called hemagglutinin and neuraminidase (Murthy *et al.* 2003). However, problems with such vaccines are their specificity to the surface proteins of special subtypes of a particular virus. As a result, they do not cross-react with other subtypes. Moreover, the rapid immunogenic alterations of influenza virus allows vaccination against solely one season's strains, and by virtue further vaccination is a of essence need in subsequent years (Leslie 2009).

In a recent study, Chen *et al.* (2009) reported a stem region of hemagglutinin that consists of a conserve fusion peptide shared across several influenza subtypes. These findings provide clear evidence that the human immune system can recognize and produce a neutralizing antibody responsive to such conserved epitope (Chen and Subbarao 2009), nevertheless further investigations are needed to determine how the conserved epitope of hemagglutinin could be used as a part of vaccination modality against influenza viruses.

Despite exploitation of vaccine therapy modalities, there are many problems for simple implementation of such therapeutics. For instance, Crowe and other flu experts caution that production of protein based vaccine is intricate and prohibitively costly process (Leslie 2009).

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Besides, continuation of low immunization coverage in hard-to-reach areas, wastage of high-priced vaccine in traditional multi-dose presentation, failure of governments or donor partners to continue bearing the cost, managerial burden of the vaccine preparation and cold chain make the vaccine therapy much more problematic. An appropriate bioshuttle, therefore, may confer a safe, simple and efficient means for vaccine administration (Lloyd 2000).

The hypothesis

To tackle such problem, in post-genomic era, authors declare that transgenic *Hirudo medicinalis* can be exploited as a rapid microproducer of viral proteins for in-house mass vaccination. This transgenic bioshuttle could impart the necessary proteins, including those naturally presented in leech's saliva. Many of the agents in leech's saliva such as hiridin (the most potent naturally occurring known inhibitor of thrombin composing 10% of a leech head) may not be essential for biting and vaccine delivery. Thus, replacing these genes with the target fragment (i.e., stem region of the hemagglutinin containing conserve fusion peptide) can convey the desired protein with less possibility of hypersensitivity reactions (Nowak and Schrör 2007; Yantis *et al.* 2009), at which the saliva of a leech may serve as a mass flu vaccine. The use of medicinal leech, *Hirudo medicinalis*, has been validated in the modern medicine to decongest venous congestion in microvascular free flaps or replants (Granzow *et al.* 2004). Leech therapy involves several steps: a) an initial bite which is usually painless injection of saliva that contains several anticoagulant and anti-platelet aggregation substances, the best characterized and described being hirudin, b) an attachment period, during which the leech sucks blood, and c) a post-attachment period, during which the site continues to bleed (Nowak and Schrör 2007; Yantis *et al.* 2009).

Evaluation of the hypothesis

Interruption of anticoagulant genes with the antigen coding fragment would be valuable for many purposes; by insertion of the fragment in the hot spot area of the genome the transcription rate of the cloned gene could be satisfactory (Scherdin *et al.* 1990). Furthermore, the encoded protein as a secretary protein will be available in the leech's saliva and finally, excessive bleeding which occur with current leech therapy would be controlled due to the deletion of anticoagulant genes (Nowak and Schrör 2007). Tagging of humuglutenin gene by GFP as a marker of gene expression, in post transcriptional level could be exploited as an *in vivo* screening of immunogenic harboring leech, and accordingly make distinguished modified leech from native one (Cabantous and Waldo 2006). This type of vaccine delivery could be exploited as a new mass vaccination weapon in the battle against influenza especially for the people living in the developing countries with poor health conditions such as Africa, Asia and South America. It's worth noting that influenza here was presented as representative of many other diseases nevertheless we believe this novel vaccination method would be successfully established for any serious diseases.

Consequences of the hypothesis and discussion

The biggest concern of this method is inadequate or extra vaccine transferring through the penetration process which results in receiving little antigen or hypersensitivity reactions respectively. Compensations of these issues could be carried out using the number of leeches to be applied and the frequency of the therapy. In addition, Immunogenicity toward artificial protein is influenced by numerous characteristics of an antigen such as molecular size, epitope density, chemical composition and heterogeneity, degradability (ability to be processed and presented to T cells) which all could be implemented using suitable genetic manipulation of protein as an immunogene (Abbas 2009).

Ethical issues

None to be declared.

Conflict of interests

No conflict of interest to be declared.

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