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Antiviral Neutralizing Antibodies from *Vitro* to *Vivo* Action

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INTRODUCTION

Neutralizing antibodies (nAbs) are being increasingly used as passive antiviral reagents in prophylactic and therapeutic modalities and to guide viral vaccine design. *In vivo*, nAbs can mediate antiviral functions through several mechanisms, including neutralization, which is defned by *in vitro* assays in which nAbs block viral entry to target cells, and antibody efector functions, which are defned by *in vitro* assays that evaluate nAbs against viruses and infected cells in the presence of effector systems. Interpreting *in vivo* results in terms of these *in vitro* assays is challenging but important in choosing optimal passive antibody and vaccine strategies. The COVID-19 pandemic has introduced the concept of neutralizing antibodies (nAbs) to the lay public and raised the profile of such antibodies in the scientific community generally. As is the case for many viruses, there is a fairly good correlation between levels of serum nAbs, as identified by *in vitro* assays, and protection against infection and disease for SARS-CoV-2, the virus that causes COVID-19. However, there are many misconceptions about nAbs and how they function. The term 'neutralizing' might be taken to indicate that these antibodies function *in vivo* predominantly by neutralization (as defined below), but this is not necessarily the case. Furthermore, there is great heterogeneity in the mechanism(s) of action of individual nAbs, even those that are apparently closely related. Much information has accumulated recently on nAbs to a wide range of viruses, which can be used to gain a better understanding of their activities. There are several definitions of neutralization, two of which are widely accepted.

DESCRIPTION

The phrase "without the involvement of any other agency indicates that neutralization is typically measured *in vitro* by incubating antibodies, virus particles and target cells together and demonstrating reduced infection. A second definition of neutralization is "the reduction in viral infectivity by the binding of antibodies to the surface of viral particles (virions), thereby blocking a step in the viral replication cycle that precedes virally encoded transcription or synthesis. For enveloped viruses, this block occurs before virus entry into a host cell but for non-enveloped viruses, it can occur after entry. In both cases, neutralization according to these definitions can be measured in *in vitro* assays. However, the term 'neutralization' can also be used to describe antiviral activities of antibodies such as protection *in vivo*, which may or may not involve neutralization in terms of blocking viral entry. This has created considerable confusion in the literature when antiviral ('neutralizing') activity *in vivo* is mediated by antibodies that do not block viral entry in typical neutralization assays *in vitro* in other words, non-neutralizing antibodies (nnAbs). For the most part, the field has chosen to avoid confusion by defining neutralization so that it can be assessed by typical *in vitro* assays, involving antibody, virus and target cells alone [1-4].

CONCLUSION

The ability of nAbs to block viral entry by enveloped viruses *in vitro* requires that the antibodies bind to functional entry molecules on the surface of infectious virions, typically envelope (Env) protein spikes. Binding to these functional structures also endows nAbs with many other potential antiviral activities that could be manifested *in vivo* but are not present in neutralization assays *in vitro*. It is in the nature of science to seek to discern patterns and establish rules but nAbs and viruses are very diverse and generalizations about theinterplay between the two are to be treated with caution.

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CONFLICT OF INTEREST

The author declares there is no conflict of interest in publishing this article.

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