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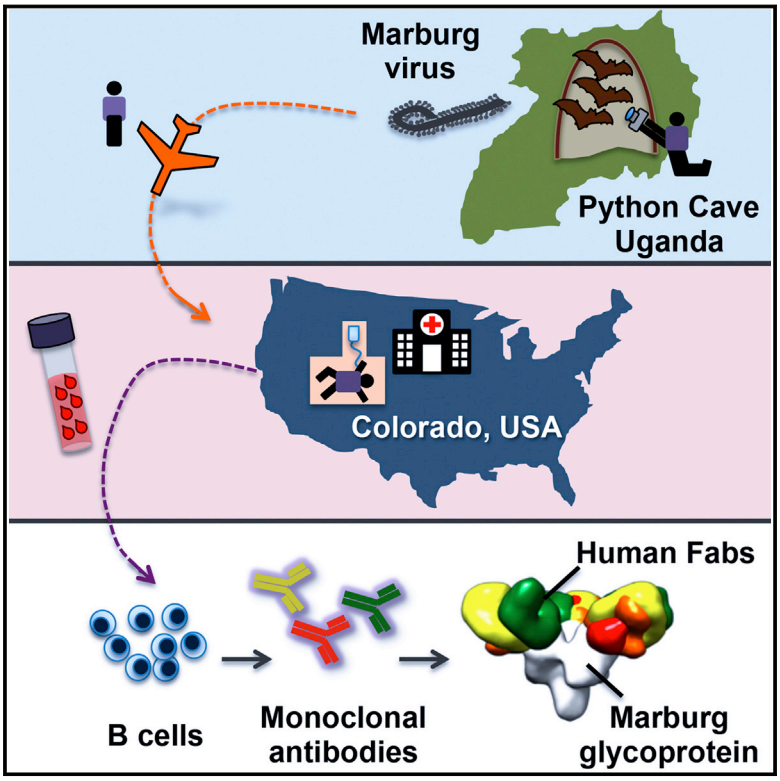
Mechanism of Human Antibody-Mediated Neutralization of Marburg Virus

Graphical Abstract



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In Brief

The characterization of Marburg-specific antibodies in several patients who survived the infection reveals a common binding site in the viral glycoprotein and a mechanism for filovirus inhibition.

Highlights

- Marburg virus survivor-neutralizing antibodies bind to a single antigenic site
- Several of the survivors' antibodies also bind to Ebola virus glycoprotein
- All antibodies identified bind at the predicted region of the receptor-binding site
- Binding to receptor-binding site is a new mechanism of filovirus inhibition

Flyak et al., 2015, Cell *160*, 893–903
February 26, 2015
http://dx.doi.org/10.1016/j.cell.2015.01.031

CellPress

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Mechanism of Human Antibody-Mediated Neutralization of Marburg Virus

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http://dx.doi.org/10.1016/j.cell.2015.01.031

SUMMARY

The mechanisms by which neutralizing antibodies inhibit Marburg virus (MARV) are not known. We isolated a panel of neutralizing antibodies from a human MARV survivor that bind to MARV glycoprotein (GP) and compete for binding to a single major antigenic site. Remarkably, several of the antibodies also bind to Ebola virus (EBOV) GP. Single-particle EM structures of antibody-GP complexes reveal that all of the neutralizing antibodies bind to MARV GP at or near the predicted region of the receptor-binding site. The presence of the glycan cap or mucin-like domain blocks binding of neutralizing antibodies to EBOV GP, but not to MARV GP. The data suggest that MARV-neutralizing antibodies inhibit virus by binding to infectious virions at the exposed MARV receptor-binding site, revealing a mechanism of filovirus inhibition.

INTRODUCTION

Marburg virus (MARV) and Ebola virus (EBOV), which are members of the family *Filoviridae*, infect humans and non-human primates, causing a hemorrhagic fever with mortality rates up to 90% (Brauburger et al., 2012). There have been a dozen outbreaks of Marburg virus infection in humans reported to date, including the most recent report from Uganda of a 30-year-old male health worker who died in September 2014 (WHO, 2014a). As of January 7, 2015, there have been in excess of 20,000 confirmed, probable, and suspected cases of Ebola virus disease (EVD) in the current EBOV outbreak in nine affected countries (Guinea, Liberia, Mali, Nigeria, Senegal, Sierra Leone, Spain, the United Kingdom, and the United States of America), with more than 8,000 deaths (WHO, 2014b).

There is no licensed treatment or vaccine for filovirus infection. Recently, several studies showed that filovirus glycoprotein (GP)-specific neutralizing antibodies (nAbs) can reduce mortality following experimental inoculation of animals with a lethal dose of EBOV (Dye et al., 2012; Marzi et al., 2012; Olinger et al., 2012; Qiu et al., 2012, 2014; Pettitt et al., 2013) or MARV (Dye et al., 2012). The primary target of these nAbs, the filovirus surface GP, is a trimer composed of three heavily glycosylated GP1-GP2 heterodimers (Figure S1). The GP1 subunit can be divided further into base, head, glycan cap, and mucin-like domains (Lee et al., 2008). During viral entry, the mucin-like domain and glycan cap mediate binding to multiple host attachment factors present on the cell membrane. After the virus enters the host cell by macropinocytosis (Nanbo et al., 2010; Saeed et al., 2010), the GP is cleaved by host proteases that remove approximately 80% of the mass of the GP1 subunit, including the mucin-like domain and glycan cap (Chandran et al., 2005; Dube et al., 2009). After cleavage of GP in the endosome, the receptor-binding sites on GP become exposed, and the GP1 head then is able to bind to its receptor, Niemann-Pick C1 (NPC1) protein (Carette et al., 2011; Chandran et al., 2005; Côté et al., 2011). Subsequent conformational changes in GP facilitate fusion between viral and endosomal membranes.

The dense clustering of glycans on the glycan cap and mucin-like domain likely shield much of the surface of EBOV GP from humoral immune surveillance, leaving only a few sites on the EBOV GP protein at which nAbs could bind without interference by glycans (Cook and Lee, 2013). Most of our knowledge about humoral response against filovirus infections has come from studies of murine Abs that recognize EBOV GP. From those studies, we learned that mouse nAbs preferentially target peptides exposed in upper, heavily glycosylated domains or lower areas (the GP1 base), where rearrangements occur that drive