Development of Cysteine Cathepsin Inhibitors as Anti-Ebola Virus Agents

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Ebola and Marburg filoviruses are enveloped negative-stranded RNA viruses that cause rapidly fatal hemorrhagic fever in humans. Previously, we identified the acid-dependent endosomal cysteine protease cathepsin B (Cat B) as an essential host factor for infection of Vero cells by Ebola Zaire. More recently, we have shown that Cat B and the related protease cathepsin L are also essential host factors for Ebola Cote d'Ivoire, Sudan, and Reston viruses and Marburg (Musoke) viruses. Our studies indicate that the filovirus glycoprotein GP is the target for proteolytic cleavage by these enzymes during infection. GP is a trimer of dimers (GP1 and GP2) that is similar in organization and function to other "Type I" envelope glycoproteins including influenza hemagglutinin and retrovirus Env. Using selective inhibitors and protease deficient cells, we show that activation of virus membrane fusion and infection is dependent on sequential cleavage of GP1 to remove domains that stabilize the pre-fusion conformation of GP2 and/or to expose a receptor binding domain. Therefore, the role of endosomal cysteine proteases in filovirus infection is analogous to CD4/co-receptor binding to gp120 in HIV infection. Importantly, inhibitors of endosomal cysteine proteases prevent transmission/spread of Ebola and Marburg viruses and therefore are potential anti-viral agents.