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Novel Antiviral Therapy Based on Innate Immunity

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Orthopox viruses include variola major (the etiologic agent for smallpox), vaccinia virus (VV), and monkeypox. Although the devastating effects of smallpox have been successfully controlled by vaccination with VV, vaccine programs have been discontinued, raising the population's susceptibility to VV bioterrorism. Furthermore, immunocompromised individuals and those with atopic dermatitis are at risk for fatal complications of vaccination, such as progressive vaccinia and eczema vaccinatum, respectively (Cono *et al*., 2003).

Despite the effectiveness of intravenous Ig and other antiviral therapies, treatment of orthopox infections is imperfect. The innate immune system produces antimicrobial compounds such as human β-defensins and cathelicidins, which exhibit antiviral activity against VV (Howell *et al*., 2007). In addition, innate immunity in patients with atopic dermatitis has been found to be deficient. This may, in part, predispose these individuals to develop eczema vaccinatum. Therefore, peptides such as human β-defensin-3 might represent a potential treatment for these adverse reactions; however, rapid degradation by endogenous tissue proteases occurs when peptides are introduced systemically. Structurally similar to antimicrobial peptides and able to selectively disrupt bacterial cell walls, a novel class of synthetic compounds called ceragenins (CSAs) shows promise as a therapeutic agent against orthopox virus infections (Ding *et al*., 2004).

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To elucidate the salutary properties of CSAs, Howell and colleagues (2009, this issue) conducted a series of *in vitro* and *in vivo* experiments to assess the ability of various CSAs to destroy VV, restore and protect keratinocytes, and limit systemic viral dissemination; they also studied the mechanisms by which CSAs might work. CSA-13 was found to be the most potent of the CSAs studied, exhibiting *in vitro* antiviral activity and efficacy as a topically applied cream. The effects of CSAs might be multimodal, affecting viral propagation by disrupting the viral envelope and stimulating the activity of other antimicrobial peptides against VV.

Through the following questions, we examine this paper in greater detail. For discussion and brief answers, please refer to the supplementary information linked to the online version of the paper at http://www.nature.com/jid.

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QUESTIONS

1. Why are orthopox virus infections important?
2. What are ceragenins?
3. What studies were carried out to determine whether ceragenins effectively combat orthopox virus infections?
4. What were the major findings of this study?
5. What were the limitations of the study?
6. What are the implications of this article?

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