J. Comp. Path. 2013, Vol. 148, 6–21

Available online at www.sciencedirect.com

SciVerse ScienceDirect

ELSEVIER

www.elsevier.com/locate/jcpa

INFECTIOUS DISEASE: REVIEW ARTICLE

Comparative Pathology of Smallpox and Monkeypox in Man and Macaques

J. A. Cann*, P. B. Jahrling*, L. E. Hensley† and V. Wahl-Jensen*

** Integrated Research Facility at Fort Detrick, Division of Clinical Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 8200 Research Plaza and † US Army Medical Research Institute for Infectious Diseases, Fort Detrick, Frederick, MD, USA*

Summary

In the three decades since the eradication of smallpox and cessation of routine vaccination, the collective memory of the devastating epidemics caused by this orthopoxvirus has waned, and the human population has become increasingly susceptible to a disease that remains high on the list of possible bioterrorism agents. Research using surrogate orthopoxviruses in their natural hosts, as well as limited variola virus research in animal models, continues worldwide; however, interpretation of findings is often limited by our relative lack of knowledge about the naturally occurring disease. For modern comparative pathologists, many of whom have no first-hand knowledge of naturally occurring smallpox, this work provides a contemporary review of this historical disease, as well as discussion of how it compares with human monkeypox and the corresponding diseases in macaques.

Keywords: macaque; monkeypox; smallpox; variola

Contents

Correspondence to: J. A. Cann (e-mail: cannja@niaid.nih.gov).

0021-9975/$ - see front matter
http://dx.doi.org/10.1016/j.jcpa.2012.06.007

Introduction

Renewed interest in the development of medical countermeasures against smallpox, and to a lesser extent monkeypox, has led to an increased use of macaque models of both diseases. These models are used at all stages of the research process, from basic mechanistic investigations to regulatory safety and efficacy evaluations (Huggins *et al*., 2009; Jordan *et al*., 2009; Shao *et al*., 2009; Keasey *et al*., 2010; Zielinski *et al*., 2010; Estep *et al*., 2011; Hirao *et al*., 2011). In the USA, regulatory clearance of new countermeasures requires that the compound in question be tested in accordance with the 'Animal Rule' (FDA 21 CFR 601.90). Thus, an animal model that accurately recapitulates the human condition is needed for both the identification and testing of therapeutic targets. Macaques have been used in studies employing both variola virus (VARV) and monkeypox virus (MPXV) delivered by different routes, yet it is largely unclear how the resultant systemic pathology compares with that of the naturally occurring disease. To this end, we provide a comprehensive review of the pathology of human smallpox and a detailed analysis of how it compares with human monkeypox and the various macaque models of smallpox and monkeypox.

Virology

The family *Poxviridae* is comprised of complex double-stranded DNA viruses whose replication cycle occurs exclusively within the cytoplasm of host cells. The family is divided further into two subfamilies, Chordopoxvirinae and Entomopoxvirinae based on the ability to infect vertebrate or insect cells, respectively. VARV and MPXV are classified in the *Orthopoxvirus* genus, one of eight genera within the Chordopoxvirinae subfamily. While VARV and MPXV are genetically and antigenically related, these viruses differ in sequence within regions encoding virulence and host-range factors near the genome termini (Shchelkunov *et al*., 2001). Comparative genomics of 45 epidemiologically varied VARV isolates indicate low sequence diversity (Esposito *et al*., 2006). However, comparison of VARV strain Japan 1951 (Harper masterseed) and MPXV strain Zaire-96-I-16 shows that the MPXV genome is 10,678 base pairs larger than that of VARV (Shchelkunov *et al*., 2001; Esposito *et al*., 2006). In addition, comparison of VARV strains India-1967 and Bangladesh-1975 with MPXV strains Zaire-96-I-16 and Congo-8 shows that the MPXV genomes have mutations that affect translation of two interferon resistance genes that encode proteins (C3L and E3L) that are intact in VARV (Shchelkunov *et al*., 2001). The MPXV genomes also encode a secreted interleukin (IL)-1β-binding protein, which the VARV genomes do not (Shchelkunov *et al*., 2001). Deletion of this gene in vaccinia virus has been correlated with increased pathogenicity (Alcami and Smith, 1996). Genomic differences are important when one considers using MPXV as a surrogate model for VARV, particularly with respect to testing of vaccines and therapeutic countermeasures. Such variation could result in appreciable differences in pathogenesis in different hosts.

In addition to molecular differences, MPXV and VARV have dissimilar host ranges. Prior to eradication VARV was distributed worldwide throughout the human population only, and the lack of an animal reservoir contributed to the success of its eradication (Fenner *et al*., 1988c). MPXV is restricted to western and central Africa, which reflects, in part, the geographical distribution of its rodent reservoir hosts (Essbauer *et al*., 2010). Multiple ecological surveys have implicated African rodents, including *Funisciurus* spp., *Heliosciurus* spp., and *Cricetomys* spp., and not non-human primates as the natural reservoir hosts of MPXV (Khodakevich *et al*., 1986, 1987, 1988; Hutin *et al*., 2001). In addition, an outbreak of monkeypox, which occurred in the USA in 2003 was associated with the importation of rodents from Ghana, West Africa (Annonymous, 2003; Reed *et al*., 2004).

Smallpox in Man

Classification and Disease Course

Human smallpox presented with varying clinical patterns, historically giving rise to numerous