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Review

Myxomatosis in Australia and Europe: A model for emerging infectious diseases

Peter J Kerr *

CSIRO Ecosystem Sciences, GPO Box 1700, Canberra, ACT 2601, Australia

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ABSTRACT

Myxoma virus is a poxvirus naturally found in two American leporid (rabbit) species (*Sylvilagus brasiliensis* and *Sylvilagus bachmani*) in which it causes an innocuous localised cutaneous fibroma. However, in European rabbits (*Oryctolagus cuniculus*) the same virus causes the lethal disseminated disease myxomatosis. The introduction of myxoma virus into the European rabbit population in Australia in 1950 initiated the best known example of what happens when a novel pathogen jumps into a completely naïve new mammalian host species. The short generation time of the rabbit and their vast numbers in Australia meant evolution could be studied in real time. The carefully documented emergence of attenuated strains of virus that were more effectively transmitted by the mosquito vector and the subsequent selection of rabbits with genetic resistance to myxomatosis is the paradigm for pathogen virulence and host–pathogen coevolution. This natural experiment was repeated with the release of a separate strain of myxoma virus in France in 1952. The subsequent spread of the virus throughout Europe and its coevolution with the rabbit essentially paralleled what occurred in Australia. Detailed molecular studies on myxoma virus have dissected the role of virulence genes in the pathogenesis of myxomatosis and when combined with genomic data and reverse genetics should in future enable the understanding of the molecular evolution of the virus as it adapted to its new host. This review describes the natural history and evolution of myxoma virus together with the molecular biology and experimental pathogenesis studies that are informing our understanding of evolution of emerging diseases.

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* Tel.: +61 2 62464334; fax: +61 2 62464094.
E-mail address: peter.kerr@csiro.au

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1. Introduction

The modern world has seen an ever expanding number of novel diseases of humans and animals (Jones et al., 2008; Keesing et al., 2010). Understanding and predicting the outcome of emerging pathogens is not easy and is likely to differ in each case. Infectious diseases such as malaria, smallpox, tuberculosis and bubonic plague have had a major impact on human populations and at least some infectious diseases appear to have influenced human gene frequencies (Dobson and Carper, 1996; Hill, 2006; Vannberg et al., 2011); the outcome of the current AIDS pandemic on human genetics can only be speculated. Good mammalian models for natural selection by pathogens are uncommon but there is one example of a massive biological experiment that was replicated on two continents, this is the release of myxoma virus (MYXV), the cause of myxomatosis, as a biological control for the European rabbit (*Oryctolagus cuniculus*) in Australia and subsequently in Europe (Fenner and Fantini, 1999). The shift in species, initial extreme virulence and subsequent host–pathogen coevolution, in a species with prolific reproduction and short generation time, plus the ability to undertake experimental studies in the same host species, made myxomatosis the classic paradigm for what happens as an emerging pathogen adapts to a new host. In particular, the nexus between virulence and transmission overturned the cosy idea that pathogens should adapt to cause minimal harm to their hosts (Anderson and May, 1982; Massad, 1987; Dwyer et al., 1990). More recently, molecular and genomic studies offer the prospect of understanding the molecular basis of this evolution.

This review firstly describes the natural history of MYXV, its use as a biological control and subsequent host–pathogen coevolution in Australia and Europe. It then turns to the pathogenesis of MYXV and the current knowledge of MYXV genes and the experimentally defined or inferred functions of the encoded proteins for pathogenesis. Finally, the current and future evolution of myxoma virus is briefly examined.

2. Natural history of myxoma virus

2.1. Myxomatosis

Myxomatosis was originally described following an outbreak of a novel lethal disease in laboratory rabbits at the Institute of Hygiene in Montevideo, Uruguay in 1896 (Sanarelli, 1898; Fenner and Ratcliffe, 1965), although the disease was apparently known to rabbit breeders (Aragão, 1927), and subsequently investigated following outbreaks at the Institute Oswaldo Cruz in Brazil (Moses, 1911; Aragão, 1927; Fenner and Ratcliffe, 1965). These were European rabbits (*O. cuniculus*), the common domestic and laboratory rabbit, which are not native to the Americas. Sanarelli (1898) suggested that the disease was due to a virus, making myxomatosis one of the earliest diseases of animals to be associated with a virus. Sanarelli was unsuccessful at infecting other species, including humans, by inoculation of infectious material from the diseased rabbits although he believed that an inoculated dog developed mammary tumours because of the virus (Hobbs, 1928).

Clinical signs of myxomatosis in rabbits can be observed from about 4 days after infection with virulent virus, initially as conjunctival inflammation accompanied by an elevated rectal temperature; a raised cutaneous lesion at the inoculation site may be visible but in natural infections this may not be noticed. By 6 days, anogenital swelling is present and cutaneous papular secondary lesions can be seen on the face and ears; serous and later mucopurulent discharge from the nostrils and conjunctivae becomes increasingly prominent (Fenner and Ratcliffe, 1965; Best and Kerr, 2000). Rabbits with typical acute late stage myxomatosis 8–10 days after infection have a swollen head and face, swollen drooping ears, mucopurulent blepharoconjunctivitis with swollen, closed eyelids and mucopurulent rhinitis with occlusion of the nasal passages (Fig. 1A). There are multiple discrete cutaneous swellings (sometimes termed tumours or myxomas) ranging from a few millimetres to several centimetres in diameter over the body (Fig. 1B and D). The anogenital region is grossly swollen and