Can you discuss the origins of your research related to the consequences and underlying mechanisms of cross-species transmission of viruses for the infected accidental host?

AV: Our lab has always been studying host-pathogen interactions, addressing both fundamental and applied questions related to this topic. The decision to study malignant catarrhal fever (MCF) induced by alcelaphine herpesvirus 1 (AlHV-1) took place in 2002. We found it fascinating that a virus can be apathogenic for its natural host and lethal for susceptible non-natural contaminated host species. We also found the pathogenesis of MCF irresistible to study because of its prolonged asymptomatic incubation period followed by an acute development leading to the death of the animal. Additionally, the lesions associated with MCF are unusual, revealing the infiltration of most organs by cytotoxic lymphoblastic cells. In addition to our interest as a fundamental model, MCF also has an important societal impact in some regions of the world, thereby representing an interesting subject for applied research.

You suggest that the relationship between AlHV-1 and its natural wildebeest host can be defined as symbiotic. Can you provide examples of some of the ways in which each species benefits?

AV: Symbiosis can be defined as the reciprocal beneficial association of two biological entities. On the one hand, AlHV-1 takes advantage of its adaptation to its host, relying on its apathogenic spread throughout the host population and latent infection to persist. On the other hand, wildebeest benefit from MCF induction in susceptible ruminant competitor species. Induction of MCF in susceptible species would have two indirect positive effects for the wildebeest population. Firstly, it would provide access to more food by killing species competing for grass. Secondly, weakened sick animals developing MCF represent easy prey for large predators thereby reducing the pressure of predation on wildebeest calves. Based on these arguments, we could define the relationship between AlHV-1 and wildebeest as symbiotic.

What do you mean by the term 'latent infection' and can you elaborate on why your research suggests that it is essential for MCF induction?

BD: Although AlHV-1 does replicate in bovine cell lines in vitro, it quickly loses its virulence after prolonged propagation. In order to target genes of interest in the viral genome, and to overcome the possible loss of virulence, we generated and used an infectious and pathogenic bacterial artificial chromosome of the entire viral genome, which is now used extensively in our studies on the pathogenesis of MCF and enables the generation of recombinant viruses in only a few weeks.

Why did you choose rabbit as the species in which to experimentally study MCF?

BD: Small animal models are extensively used in fundamental research, particularly mice. However, mice are not susceptible to AlHV-1 intra-nasal infection; nor are rats, guinea pigs or hamsters. Rabbits, on the other hand, are very susceptible to virus infection and reproduce a pathology that is very similar to the disease observed in cattle. Although boids are the most relevant species to experimentally study the pathogenesis of MCF, rabbit represents a reliable and easy to handle animal model that can address the roles of particular virus genes in the development of MCF.
MALIGNANT CATARRHAL FEVER (MCF) is a fatal disease characterised by a strong and prolonged fever, associated with abundant nasal and ocular discharges. It affects numerous ruminant species including, but not limited to, cattle, bison and banteng, and it is generally true that the longer an animal survives the symptoms of MCF, the more severe they become. This helps to explain why the disease has a mortality rate close to 100 per cent. As the ailment is caused by alcelaphine herpesvirus 1 (AlHV-1), which has a symbiotic relationship with wildebeest, it is unsurprising that regions inhabited by this animal have the highest incidence of MCF in closely related species of domesticated livestock.

The farmers that work in these areas – mainly in eastern and southern Africa – suffer dramatically from the economic impact of the death of large numbers of valuable livestock after contracting this disease. One group of people who are particularly affected are the Maasai, who often rely on livestock as their sole source of income. Some reports have suggested that about 7-13 per cent of Maasai cattle herds exposed to wildebeest develop MCF per year, which could represent annual losses of around half a million animals. However, it is challenging to obtain a reliable estimate for this number as animals that become sick are rapidly sold without reporting the disease.

Recent participatory studies in Tanzania and Kenya have shown that the local pastoralists perceive MCF as a high impact disease in the same category as East Coast fever and foot-and-mouth. MCF has also gained significance for the damage it has caused to zoological collections, which include high value and sometimes endangered susceptible species.

FROM THESIS TO APPLICATION

Dr Benjamin Dewals focused his PhD thesis on the pathogenesis of MCF, during which time he made a number of substantial breakthroughs in the area. Under the supervision of Dr Alain Vanderplasschen, Dewals demonstrated that the onset of MCF disease is associated with an exponential increase of viral DNA in peripheral mononuclear blood cells, while infectious particles could not be isolated from these cells. This suggests that the pathology could be the acute expression of a latent-based disease, an idea upon which they have built their ongoing research. Dewals has continued working with Vanderplasschen on this area of research and, with input from the PhD students and postdoctoral researchers he now supervises, they have further developed the concepts, questions and potential applications raised by his PhD investigations.

One interesting observation that the team has worked towards understanding is that transmission rates of AlHV-1 are at their highest during wildebeest calving season. This is likely to occur as a consequence of the symbiotic evolution of the two species, as increased disease transmission during this period will lead to calves being more likely to survive and pass on their genes. This co-evolution with their host species is typical of herpesviruses. As a consequence of this rationale, transmission – particularly across species – has become an area of interest for the group.

TRANSMISSION

It has been shown that the seroprevalence of AlHV-1 in wildebeest is greater than
With more than 400,000 wildebeest calves born each year in East Africa alone, it is clear that the infection of domestic cattle is unlikely to decrease without the use of a vaccine. 90 per cent, which has led to the assumption that the entire wild population of the species is infected. However, because the virus remains latent for the majority of its natural host’s life, transmission is not likely at all times. It is generally accepted that the major pathway for infection is through nasal and ocular secretions – although one report does implicate vector-borne transmission. Viral particles have been detected in the nasal and ocular secretions of wildebeest calves during the first six to nine months of their life. It is also acknowledged that transmission from mother to calves occurs during this time, also via these discharges. This goes a long way towards explaining the periodicity of the rate of infection.

With more than 400,000 wildebeest calves born each year in East Africa alone, it is clear that the infection of domestic cattle is unlikely to decrease without the use of a vaccine. In an attempt to develop this much needed method of immunisation, further development of a model for pathogenesis is required. For example, the exact mechanism by which MCF leads to the death of infected non-natural host species is not yet clear. However, because this is a much pursued avenue of research, the results have highlighted a number of previously uncharacterised symptoms. Some key effects of the disease that may be involved in non-natural host pathogenesis are generalised enlargement of lymph nodes and spleen, and infiltration of proliferating lymphoproliferative T cells in the perivascular spaces throughout the body of the affected animal. Additionally, it has been shown that self-cytotoxic reactions and cytokine storms are involved in some way. It is also not yet fully understood why symptomatic MCF does not develop in wildebeest, despite the large similarity with other species for which the disease is fatal.

MODEL OF PATHOGENESIS

Through various experimental approaches, and over a number of years, the team from Liège has developed a thorough understanding of certain aspects of the pathogenesis of MCF. The most useful advances have come from the identification of particular proteins and cell markers that are fundamental to the development of MCF and the life cycle of AlHV-1. They have shown, for instance, that the latency site of the virus is in a population of T cells expressing the CD8 marker, in which no viral particles are produced but infected cells undergo uncontrolled proliferation. During this latency-induced proliferation, the viral genome is maintained as circular episome, the persistence of which is mediated by a specific genome maintenance protein encoded by ORF73. The expression of this protein has been shown to be essential for MCF development. These biomolecules and the biological activity they induce may clearly be linked to future attempts at vaccine development.

Despite these progressive findings, a number of key gaps remain in the group’s understanding: the cell type in which the virus initially replicates upon infection and the mechanisms by which it induces the proliferation of latently infected cells. Highlighting one particular obstacle that has slowed the group’s progress, Dewals explains: “Studying the pathogenesis of a disease caused by a gammaherpesvirus after cross-species transmission from wildebeest to cattle is, in a way, particularly challenging as it necessitates the genetic manipulation of its large genome”.

A substantial level of understanding of AlHV-1 and MCF has led to a feasible infection management technique involving the physical separation of livestock from wildebeest, particularly during calving season. However, there are a number of key aspects of the pathogenesis of MCF which are yet to be unravelled. The team remains hopeful that success is within reach, however, and further development of this project will lead to both an increased understanding of fundamental pathological concepts and the application of that understanding to develop much needed vaccine.