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SHORT COMMUNICATION

A shared unusual genetic change at the chemokine receptor type 5 between *Oryctolagus*, *Bunolagus* and *Pentalagus*

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Abstract Whereas in most leporid species studied the effects of exposure to Myxoma virus (MV) are benign, in the European rabbit (*Oryctolagus cuniculus*) it causes an epizootic disease with particularly high mortality rates, known as myxomatosis. Chemokine receptors are known to play an important role in infection by large DNA viruses such as MV, by acting as portals for viral entry into the host cell. As with the human immunodeficiency virus, CCR5 is among the major candidates to affect resistance to myxomatosis. Previous sequence comparisons of the CCR5 gene among Leporid species revealed that a drastic change occurred at the second extracellular loop which was unique to the European rabbit species. Here we report that European rabbit shares this particular alteration with two of its closest relatives: the South African Riverine rabbit (*Bunolagus monticularis)* and the Japanese Amami rabbit (*Pentalagus furnessi)*. Both species represent monotypic genera and are included in the IUCN Red List as Endangered. It would then be urgent to study the susceptibility of these species to myxomatosis. Despite the lack of direct evidence that the altered CCR5 can affect the outcome of exposure to MV, the reported findings justify preventive measures to be considered.

Keywords Chemokine receptors · Gene conversion · Myxomatosis · Riverine rabbit (*Bunolagus monticularis*) · Amami rabbit (*Pentalagus furnessi*) · European rabbit (*Oryctolagus cuniculus*)

Introduction

Infectious diseases are thought to play a major role in shaping the genetic diversity of host organisms. The myxomatosis epizootic of European rabbit (*Oryctolagus cuniculus*) is a text-book example of host-pathogen evolution. It is caused by the myxoma virus (MV), a *Poxvirus* member of the genus *Leporipoxvirus* most commonly and efficiently transmitted by mechanical transfer through insect bites (reviewed by Fenner and Ratcliffe 1965). In the natural hosts such as the jungle rabbit (*Sylvilagus brasiliensis*) of South America and brush rabbit (*Sylvilagus bachmani*) from North America, infection with MV produces only a small-localized fibroma, without generalized symptoms (Fenner and Ratcliffe 1965), whereas, in the

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European rabbit (*Oryctolagus cuniculus*) the virus causes a highly lethal disease (Fenner 1957, 1983).

Viruses can use a wide range of cellular receptors for cell binding and entry to initiate the infectious process. Human AIDS and rabbit myxomatosis share some remarkable similarities such as the induction of a systemic cellular immune dysfunction with virus dissemination through migratory leukocytes (Grist 1988; Lalani et al. 1999; Nash et al. 1999). Additionally, both viruses use members of the chemokine receptor family for entering cells and start infection (Dragic et al. 1996; Lalani et al. 1999). Among these receptors, CXCR4 and CCR5 are the major candidates to play a role in the MV infection (Lalani et al. 1999; Barrett et al. 2001). A previous study on the Lagomorph CXCR4 protein revealed little amino acid variation, except for minor changes at the intracellular loops of the rabbit CXCR4 protein (Abrantes et al. 2008). In contrast, the sequencing of the leporid CCR5 and CCR2 genes revealed that in *Oryctolagus*, the second extracellular loop of CCR5 was altered by gene conversion with CCR2, a change not found in any other mammal species (Shields 2000; Esteves et al. 2007; Vàzquez-Salat et al. 2007; Perelygin et al. 2008) including the leporid species *Sylvilagus* and *Lepus* (Carmo et al. 2006). The question was raised whether this alteration of the CCR5 protein could contribute to the susceptibility of European rabbit to myxomatosis (Carmo et al. 2006).

The order Lagomorpha is divided in two families, the Ochotonidae (pikas), with only one extant genus, *Ochotona*, and the Leporidae (rabbits and hares), which includes 11 living genera: *Brachylagus, Bunolagus, Caprolagus, Lepus, Nesolagus, Oryctolagus, Pentalagus, Poelagus, Pronolagus, Romerolagus and Sylvilagus* (Hoffmann and Smith 2005). These two families diverged around 40 million years ago (Matthee et al. 2004; Matthee 2008). The evolutionary relationships among Leporid genera have long been a contentious issue and were largely unresolved (Lopez-Martinez 1989; Corbet 1983; Dawson 1981; Halanych and Robinson 1999). More recently Matthee et al. (2004) used a molecular supermatrix combining both nuclear and mitochondrial genes and provided the first well resolved phylogeny for the group (also see Robinson and Matthee 2005 for a more comprehensive analysis). Based on nuclear DNA analyses of five fragments, these authors proposed a strongly supported monophyletic association between *Oryctolagus* and *Bunolagus* who last shared a common ancestor approximately 7–8 million years ago. This clade shares a close evolutionary association with *Caprolagus* and *Pentalagus*. Together these four genera diverged from *Sylvilagus* and *Brachylagus* at least ~10 million years ago (Fig. 1).

Bunolagus monticularis, the Riverine rabbit, is the only representative of the genus *Bunolagus*. The Riverine rabbit is an endemic species to the central Karoo region of South Africa and is one of the world's rarest mammals. In fact, this species is currently assessed as Critically Endangered on the 2008 IUCN Red List (South African Mammal CAMP Workshop 2008). *Pentalagus furnessi*, the Amami rabbit, is endemic to the Japanese islands of Amami-Oshima and Tokuno-Shima (Yamada et al. 2002) and was designated a special natural monument by the Japanese government. Currently classified as Endangered on the 2008 IUCN Red list (Yamada and Sugimura 2008), this species is considered a living fossil of the ancient rabbits that once lived on the Asian mainland.

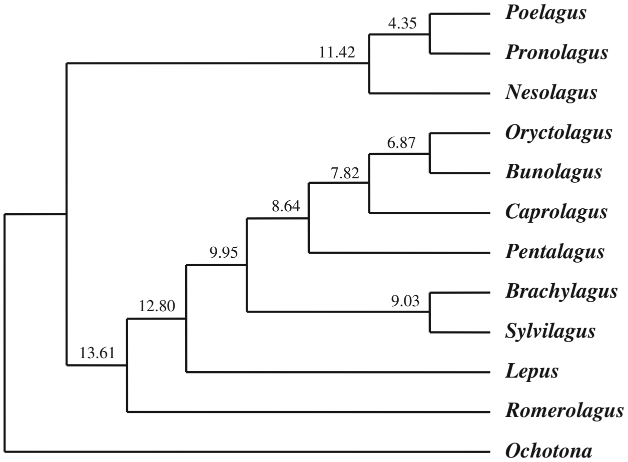

Fig. 1 Phylogeny based on data in Matthee et al. (2004) indicating the evolutionary relationships among 11 Leporid genera. The divergence time (in million years) is given for each node

In view of the monophyletic association between *Oryctolagus* and *Bunolagus* and the close evolutionary relationship with *Pentalagus*, we have extended the previous sequence determinations of the CCR5 and CCR2 genes to the genera *Bunolagus* and *Pentalagus* to assess if the gene conversion event between CCR5 and CCR2 genes is unique to the European rabbit. In addition, we have extended the characterisation of these genes to other Lagomorph species (*Lepus, Sylvilagus* and *Ochotona*).

Materials and methods

Tissue samples were obtained from wild specimens collected in Spain (*Lepus castroviejoi*), North America (*L. calotis*, *L. townsendii, Sylvilagus brasiliensis* and *Ochotona princeps*), Russia (*L. timidus*), South Africa (*L. saxatilis*) and Japan (*Pentalagus furnessi*). In the case of *Bunolagus monticularis*, DNA was obtained from a small ear piece sampled from an individual bred in captivity. In addition, samples from European rabbits (*Oryctolagus cuniculus*) collected in Australia were also used.

Genomic DNA was prepared using a Qiagen tissue extraction kit and amplification of the CCR5 and CCR2 genes was performed using the primer pairs and the PCR amplification conditions described in Carmo et al. (2006). For *Pentalagus furnessi* new primer pairs were designed: CCR5_F2 5′ ATCTTGGTGTCTCTCCCRGR 3′; CCR2_F2 5′ ATTCTCGTTACACCTGTGGC 3′ and CCR5&CCR2_R2 5′ ACCATGATGGCGAAGATGAG 3′. The forward primers were located in the 4th transmembrane domain and the reverse primer was located in the 6th transmembrane domain. For this reason, a shorter fragment (<300 bp) was obtained with these primer pairs. Sequencing was performed on an ABI PRISM 310 Genetic Analyser (PE Applied Biosystems) following the ABI PRISM BigDye Terminator Cycle Sequencing protocols. The nucleotide sequences were translated and aligned using ClustalW (Thompson et al. 1994) and adjusted by visual inspection. The inferred protein sequences were aligned with published mammal CCR2 and CCR5 sequences available in GenBank. Nucleotide sequence data obtained in this study have been submitted to GenBank. The assigned accession numbers are listed on Fig. 2

Results and discussion

The CCR5 and CCR2 exon regions sequenced cover both the second and the third intracellular cellular loops (ICL2, ICL3), and therefore ECL2. The alignment of the inferred protein sequences with published mammalian CCR5 and CCR2 sequences is shown in Fig. 2. Both *B. monticularis* and *P. furnessi* CCR5 proteins presented the same change at ECL2 (highlighted) that was previously reported for the European rabbit (Carmo et al. 2006). Like in the European

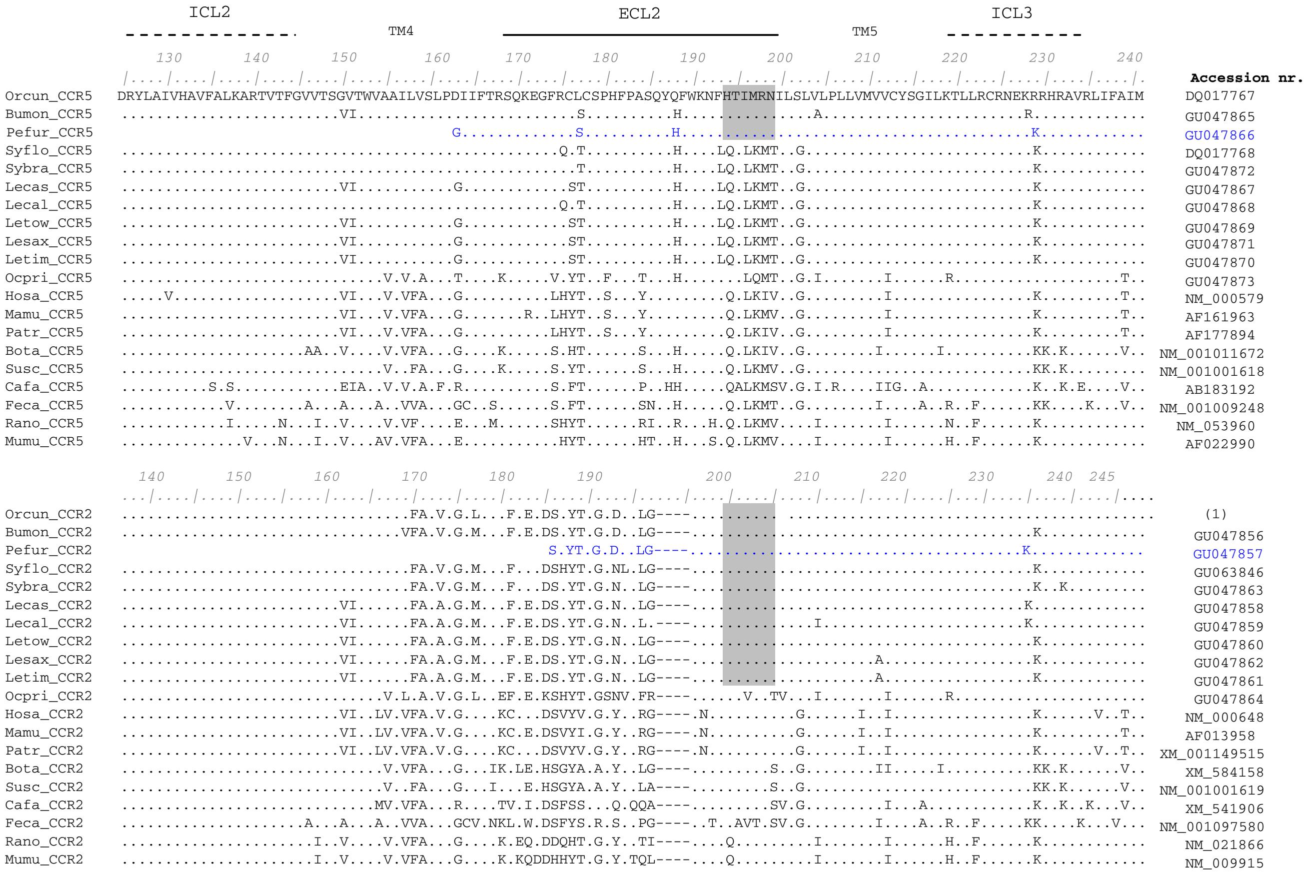

Fig. 2 Deduced protein sequences of mammalian chemokine receptors CCR2 and CCR5 aligned to CCR5 of European rabbit, Orcun_CCR5. Numbering of residue positions is according to rabbit CCR5 and CCR2 sequences, Orcun_CCR5 and Orcun_CCR2, respectively. GenBank accession numbers are listed. *Dashes* (–) represent alignment gaps; identity with the master sequence is indicated by *dots* (.), except at gap positions; (ECL) extracellular cellular and (ICL) intracellular loops. The part of ECL2 affected by the gene conversion is *shaded* in *grey*. Hosa: *Homo sapiens*; Mamu: *Macaca mulatta*; Patr: *Pan troglodytes*; Bota: *Bos taurus*; Susc: *Sus scrofa*; Cafa: *Canis familiaris*; Feca: *Felis catus*; Rano: *Rattus norvegicus*; Mumu: *Mus musculus*; Orcun: *Oryctolagus cuniculus*; Bumon: *Bunolagus monticularis*; Pefur: *Pentalagus furnessi*; Syflo: *Sylvilagus floridanus*; Sybra: *S. brasiliensis*; Lecas: *Lepus castroviejoi*; Lecal: *L. californicus*; Letow: *L. townsendii*; Lesax: *L. saxatilis*; Letim: *L. timidus*; Ocpri: *Ochotona princeps*. (1) Sequence obtained by Lu et al. (2005)

rabbit, the sequence motif $_{194}$QTLKMT$_{199}$ of the CCR5 consensus protein was replaced by the HTIMRN motif which is characteristic of CCR2. This replacement can be explained either by gene conversion in the ancestral lineage or by convergent evolution. Gene conversion would involve a single event (gene conversion between CCR5 and CCR2 in the ancestor of the three genera) whereas convergent evolution would involve three independent events, which would suggest the existence of some important benefit of this alteration to be shared among the three rabbit species. Gene conversion seems to be the most plausible explanation. The occurrence of gene conversion involving the ECL2 in *Oryctolagus*, *Bunolagus* and *Pentalagus* and its absence in all other tested mammalian species, including all other lagomorphs studied (species of *Lepus, Sylvilagus* and *Ochotona*; Carmo et al. 2006; Esteves et al. 2007; Shields 2000; Vàzquez-Salat et al. 2007), shows that this particular event has occurred prior to the *Oryctolagus/Bunolagus/Pentalagus* lineage split and most likely reflects common ancestry. Based on the dates proposed by Matthee et al. (2004) the gene conversion occurred before the lineage split of *Oryctolagus*/*Bunolagus/Pentalagus* (8.64 million years ago) and after this clade diverged from *Sylvilagus* approximately 10 million years ago (see Fig. 1). It is important to note that sequences for a larger fragment than that shown in Fig. 2 have been generated for *Bunolagus* and *Oryctolagus*. These show signatures characteristic of each gene and evidence of recombination was not detected, indicating that the two genes are distinct. Moreover, in rabbit, heterozygosity was found for both genes in the same individual. However, no heterozygosity was observed in the sequences of CCR2 and CCR5 produced for *Bunolagus*. Therefore, recombination such as found in the horse genome, for which a gene named CCR5/2 was originated by unequal crossing over between the CCR2 and CCR5 genes (Perelygin et al. 2008), is an improbable scenario causing the pattern detected.

CCR5 and CCR2 sequences were also obtained from European rabbits collected in Australia which were resistant to myxomatosis as well as from domestic and wild Portuguese rabbits that died from myxomatosis (unpublished data). All these individuals presented the CCR5 replacement. However, this observation does not exclude that CCR5 can be used by MV to infect rabbit cells. Indeed, MV has been shown to infect usually non-permissive cells after being induced to CCR5 expression (Lalani et al. 1999). Also, although MV is non-pathogenic in other vertebrates, there is growing evidence that in vitro it can infect cells from several species (Johnston et al. 2003, 2005; Sypula et al. 2004; Wang et al. 2004). Also, other Lagomorph species, which are not susceptible to myxomatosis, have been shown to be seropositive for the virus (Licón Luna 2000; Marshall et al. 1963).

The major differences found between myxomatosis-resistant and susceptible rabbits are in the inflammatory response. Indeed, in resistant rabbits it is dominated by lymphocytes and monocytes and occurs close to the virus replication site, whereas in susceptible rabbits it is predominantly composed by neutrophils and is located distantly from the site where the virus is replicating (Best and Kerr 2000; Best et al. 2000; Jeklova et al. 2008). Regarding these results, it is possible that the type and levels of expression of chemokines (rather than their receptors), which stimulate the inflammatory response, may also be related to resistance against MV by blocking chemokine receptors binding sites and thus, preventing virus infection (Best et al. 2000; Lalani et al. 1998, 1999). Also, knowing the function of the immunomodulatory gene products encoded by the genome of MV (reviewed in Zúñiga 2002) can be helpful in determining other factors that may play a role in rabbit resistance. TNF-alpha, MHC class I and IFN-gamma are possibly among these factors as they seem to be subverted by MV encoded genes (Hnatiuk et al. 1999; Upton et al. 1991; Zúñiga 2001). As MV has an array of immunoevasion strategies it is clear that resistance depends on a combination of several factors and does not exclude the chemokine receptors studied.

The small extant populations of Riverine rabbits and Amami rabbits are not expected to recover in case of myxomatosis outbreaks with mortality rates similar to that in European rabbit. Indeed, the ability of chemokine receptors to facilitate infection by MV has been shown to be non-species-specific (Lalani et al. 1999). Although no fatal cases of myxomatosis in species other than *Oryctolagus* have ever been reported, other Lagomorph species has been shown to be MV reservoirs (Licón Luna 2000; Marshall et al. 1963). Therefore, introduction of domestic rabbits into the regions occupied by these leporids should be avoided, particularly in view of the presence in South Africa of the mosquito *Aedes aegypti* (Kemp and Jupp 1991), a known vector of myxoma virus (Hagen et al. 1976).

In conclusion, we report that the Critically Endangered Riverine rabbit, the Endangered Amami rabbit and the European rabbit share an important synapomorphic change at the ECL2 of CCR5 receptor proteins, which sets these species apart from all other mammals tested, including all the other leporid taxa studied. The implications of the change in the CCR5 receptor for susceptibility to MV are currently not well understood, although the presence of the motif in the endangered Riverine and Amami rabbits as well as the susceptible European rabbit raises concern and may justify pre-emptive measures to prevent MV exposure of the endangered species.

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