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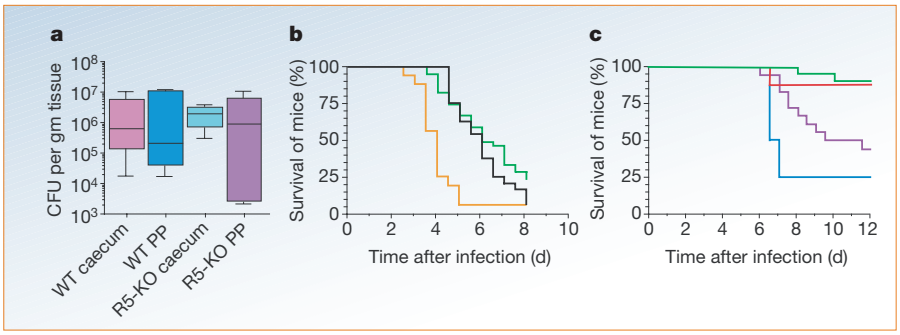

Figure 1 Impact of CCR5 deletion on the growth of *Yersinia pseudotuberculosis* and survival of mice after infection with *Y. pestis*. **a,** Bacterial growth in the caecum or in Peyer's patches (PP) of mice infected by orogastric lavage (D. Monack) with 2×10^9 *Y. pseudotuberculosis* YPIIIVV. Bacterial colony-forming units (CFU) are per g tissue at 4 days after infection. Plot shows the median, the range from 25th to 75th percentile (boxed) and the data range. WT, normal wild-type C57BL/6 mice; R5-KO, CCR5-deficient C57BL/6 mice. **b,** Comparison of survival of BALB/c mice with and without CCR5 ($n = 40$ per group), over 10 days following intravenous challenge with 10^2 *Y. pestis* KIM, substrain D27 (Pgm−, LcrV+). Green, CCR5 WT females; orange and black, CCR5-deficient males and females, respectively. **c,** Survival of mice after intravenous challenge with about ten *Y. pestis* organisms, which is close to the LD_{50} dose in this strain. Green, CCR5 WT BALB/c females; purple, CCR5 WT BALB/c males ($n = 20$ per group); red, CCR5 WT C.B-17 SCID females ($n = 8$); blue, CCR5 WT C.B-17 SCID males ($n = 4$).

Evolutionary genetics

CCR5 mutation and plague protection

A recent and prevalent mutation in the chemokine receptor CCR5 in humans of northern European ancestry has been proposed to provide protection against bubonic plague[1,2]. Here we infect both normal and CCR5-deficient mice with the bacterium *Yersinia pestis*, the cause of the plague epidemics that wiped out one-third of Europeans in the Middle Ages[3], and find no difference in either bacterial growth or survival time between the two groups. Unless the pathogenesis of *Yersinia* infection differs markedly between mice and humans, our results indicate that CCR5 deficiency in people is unlikely to protect against plague.

A 32-base-pair deletion in the coding region of *CCR5*, a mutation designated as *CCR5Δ32*, was first identified in individuals who had been exposed to HIV but who seemed to be resistant to infection[4]. This *CCR5Δ32* allele is mainly confined to caucasians[5,6], and its protective effect in homozygotes against transmission of the most common HIV-1 isolates arises because both CCR5 and CD4 are needed as co-receptors for entry of the virus into the cell.

Because the *CCR5Δ32* allele shows evidence of very strong selection, it has been suggested that it may protect against another disease associated with high mortality[1,2]. A candidate agent is *Yersinia pestis*, which emerged shortly after the estimated origin of the *CCR5Δ32* mutation (about 800 years ago), and killed some 25 million people in the Black Death plague of 1346–52.

If plague was responsible for driving this selection, the *CCR5Δ32* genotype should alter the host response to *Y. pestis* infection to improve the survival rate. But, because plague is no longer common among caucasians, the allele has not been tested for a protective effect. We therefore compared the susceptibility of two groups of mice, with and without CCR5 deficiency, to infection and death following challenge with *Yersinia*.

The homozygous *CCR5Δ32* genotype is associated with intracellular retention of a truncated CCR5 protein and ablation of the chemokine response to macrophage inflammatory protein-1β (ref. 6), whereas heterozygotes have a reduction in surface expression of CCR5 and slower progression from HIV infection to AIDS[5]. The lack of CCR5 at the cell surface has no obvious deleterious effect in humans. Mice with homozygous deletion of CCR5 have subtle immunological abnormalities, including in controlling infection by intracellular organisms such as *Listeria*, *Cryptococci* and *Leishmania*[7–9].

To test whether CCR5 deficiency protects mice against *Yersinia* infection, we challenged them with lethal inocula of wild-type *Y. pseudotuberculosis* YPIIIpYV (C57BL/6 CCR5-deficient mice) or Pgm− *Y. pestis* KIM substrain D27 (BALB/c CCR5-deficient mice). There was no significant difference in the bacterial load in the caecum or Peyer's patches at two or four days post-infection between C57BL/6 CCR5-deficient and CCR5-expressing mice following oral infection (Fig. 1a). Macrophages from CCR5-deficient animals showed little to no difference in bacterial growth of *Y. pseudotuberculosis* or *Y. pestis* compared with those from CCR5-expressing mice.

These results argue against CCR5 being essential for infection by *Y. pestis* or *Y. pseudotuberculosis*. However, they do not eliminate the possibility that a protective effect caused by CCR5 deletion may reduce mortality without changing bacterial spread. We therefore evaluated the effect of CCR5 deficiency on survival after *Y. pestis* infection in the more susceptible BALB/c mouse strain, but found no significant difference in survival between CCR5-deficient BALB/c female mice and BALB/c females with normal CCR5 expression (Fig. 1b).

Male CCR5-deficient mice survived for a shorter time (Fig. 1b; $P < 0.0001$). We therefore challenged male and female BALB/c mice with a lower dose of *Y. pestis* and again found that the males showed significantly reduced survival (Fig. 1c; $P = 0.0006$). As increased susceptibility was also seen in limited numbers of male SCID mice (Fig. 1c), this gender-related defect could be affected by innate immunity. The poorer survival of CCR5-deficient male mice (Fig. 1b) is therefore likely to be related to their gender and not to CCR5 deficiency. Gender may also be a factor in *Yersinia* infection in humans, because males seem to be more susceptible to bubonic plague than females[10].

Our results show that CCR5 deficiency in mice does not protect against infection or death caused by experimental *Yersinia* infection, making it unlikely that the *CCR5Δ32* allele protects against plague. A modelling study[11] reaches a similar conclusion, with smallpox instead of plague being proposed as the disease that selected for the *CCR5Δ32* allele.

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