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NATURE IMMUNOLOGY: INFECTIOUS DISEASE

Plague as a cause for Familial Mediterranean fever

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Evolutionary genetic and experimental analyses suggest that mutations causing Familial Mediterranean fever have been positively selected in the Middle East likely because they confer heightened resistance against *Yersinia pestis* infection.

Familial Mediterranean fever (FMF) is a common, hereditary autoinflammatory disease caused by recessive mutations in the gene encoding pyrin. FMF mainly affects populations from the Eastern Mediterranean basin, where ~8% of individuals carry one of the disease-causing pyrin variants¹. Upon bacterial infection, pyrin forms the pyrin inflammasome complex that elicits the release of pro-inflammatory cytokines and induces pyroptosis². To counteract the host response, pathogenic *Yersinia* species secrete a virulence effector, YopM, that specifically inhibits the pyrin inflammasome³. In this issue of *Nature Immunology*, Park et al.⁴ show that FMF mutations are associated with increased release of pro-inflammatory cytokines by human leukocytes and increased survival of mice upon *Y. pestis* infection. They show that FMF variants arose >1,800 years ago, prior to the first deadly plague pandemic, and have conferred a selective advantage to Middle Easterners, likely because they increase resistance to plague.

Plague pandemics were among the most devastating epidemics in the history of the northern hemisphere, causing the death of 30–60% of its total population. Because *Y. pestis* outbreaks have exerted strong selection pressure on humans, they have regularly been invoked to explain the heterogeneous geographic distribution of genetic variants associated with immune-related disease. Back in 1962, Pettenkofer et al.⁵ argued that the frequencies of the ABO histo-blood group antigens have been shaped by natural selection because they confer resistance to *Y. pestis* infection. Likewise, the high prevalence and estimated age of the *CCR5*-Δ32 variant, which protects today against HIV infection, prompted researchers to test its effects on plague susceptibility⁶. However, the evolutionary genetic and experimental analyses were debatable and subsequent studies showed that the evidence was inconclusive^{7,8}.

The role of pyrin in plague susceptibility was first proposed when a specific *Yersinia* virulence factor, YopM, was shown to inhibit the pyrin inflammasome, and be involved in the evasion of host anti-microbial responses³. YopM is secreted by pathogenic *Yersinia* species to activate the host kinases that negatively regulate pyrin by phosphorylation. The 14-3-3 proteins bind phosphorylated pyrin and block inflammasome activation, resulting in the inhibition of proinflammatory cytokine release and pyroptosis (Fig. 1). Because pyrin variants causing FMF lead to an excessive inflammasome activation², and are relatively common in regions where plague was endemic¹, researchers have hypothesized that these mutations have been selected to counteract the virulence strategy of *Y. pestis*. Nevertheless, no studies had formally investigated whether FMF-causing mutations affect the host response to *Yersinia* infection, and whether their high frequency in present-day Mediterranean populations is due to natural selection.

Using state-of-the-art approaches in evolutionary genetics, Park et al.⁴ inspected the genomic diversity of more than 2,000 individuals from Turkey to test if common amino-acid altering mutations in *MEFV*, the gene encoding pyrin, have evolved under positive selection. They found that genetic variation surrounding FMF mutations is more conserved than that surrounding random mutations at similar frequency in the Turkish population. This suggests that *MEFV* alleles have rapidly increased in frequency in the past thousand years, consistent with the action of recent positive selection⁹. By modelling the genetic diversity of the *MEFV* locus, they also estimated that the two main FMF mutations occurred ~1,800–2,600 years ago, and conferred a selective advantage that is comparable to that of the lactose tolerance allele in Europeans. Based on these results, the authors conclude that, despite their deleterious effects, FMF mutations have been under positive selection in Eastern Mediterranean populations, possibly because they confer resistance to plague. In support of this, the *MEFV* variants emerged prior to the first recorded plague pandemic, the Plague of Justinian, which began ~1,500 years ago and afflicted the entire Mediterranean Basin.

To further strengthen their hypothesis, Park et al. evaluated the protective role of FMF mutations against *Y. pestis* infection, using detailed *ex vivo* and *in vivo* experiments. They first confirmed that the *Yersinia* virulence factor YopM inhibits IL-1 β release in primed macrophages, by the pyrin inflammasome-dependent pathway. Several host protein kinases (RSK) phosphorylate pyrin only in the presence of YopM, indicating that *Yersinia* bacteria can hijack host proteins to inhibit pyrin inflammasome activation. Using pull-down assays and mutant YopM, the authors showed that YopM-induced pyrin phosphorylation requires direct interactions between YopM, pyrin and RSK proteins. Then, they explored the effect of FMF-causing pyrin mutations on *Yersinia*-host interactions. In monocytes of FMF patients infected by *Y. pestis*, the binding of YopM to pyrin and pyrin phosphorylation was reduced, relative to healthy controls. Furthermore, *Y. pestis*-induced IL-1 β

release was increased in human cells expressing pyrin with FMF mutations, compared to non-mutated pyrin (Fig. 1). Intriguingly, FMF mutations alter the C-terminal domain of pyrin, while YopM interacts directly with the N-terminal domain. Yet, the C-terminal and N-terminal pyrin domains interact together and FMF mutations reduce these interactions. Finally, knock-in mice expressing the human pyrin with FMF mutations exhibit increased survival to *Y. pestis* relative to mice expressing the non-mutated human pyrin, and survival is mediated by the IL-1 β -signalling pathway. In light of the beneficial effects of FMF mutations on the human immune response to *Y. pestis* and their recent history of positive selection, Park et al. conclude that plague epidemics have played a key role in selecting for mutations that cause today FMF in Eastern Mediterranean peoples.

Examples of beneficial mutations that confer a well-understood selective advantage are extremely rare in humans, because it is notoriously difficult to infer their evolution and effects on survival in time and space. In this study, Park et al. elegantly combined evolutionary genetic and experimental analyses to support the view that FMF-causing mutations have been positively selected to confer resistance to plague. The hypothesis is very reasonable in light of the increasing evidence supporting a role of past epidemics in selecting for mutations associated with present-day common autoimmune and autoinflammatory diseases¹⁰. Nevertheless, direct evidence is still required: the pyrin inflammasome may be repressed by other pathogens, and FMF mutations may have thus evolved under positive selection in response to other microbial pressures. Fortunately, while the task was impossible in 1962⁷, recent advances in ancient DNA sequencing now offer the unique opportunity to demonstrate the direct role of past infections on present-day disease risk. Indeed, it will soon be possible to compare the genome of victims and survivors of past pandemics and unbiasedly detect genetic variation that conferred resistance to lethal infections. Likewise, the direct measure of allele population frequencies in time and space will greatly facilitate the inference of natural selection¹¹. Finally, infection experiments with pathogens engineered to resemble those isolated from victims of pandemics¹² will offer promising new avenues for research on the evolution of microbial virulence. Collectively, there is no doubt that the study by Park et al. will stimulate new work and ideas to increase our understanding of the causes and consequences of historical epidemics such as those caused by plague, whose re-emergence poses today a significant health risk¹³.

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Competing interests

The author declares no competing interests.

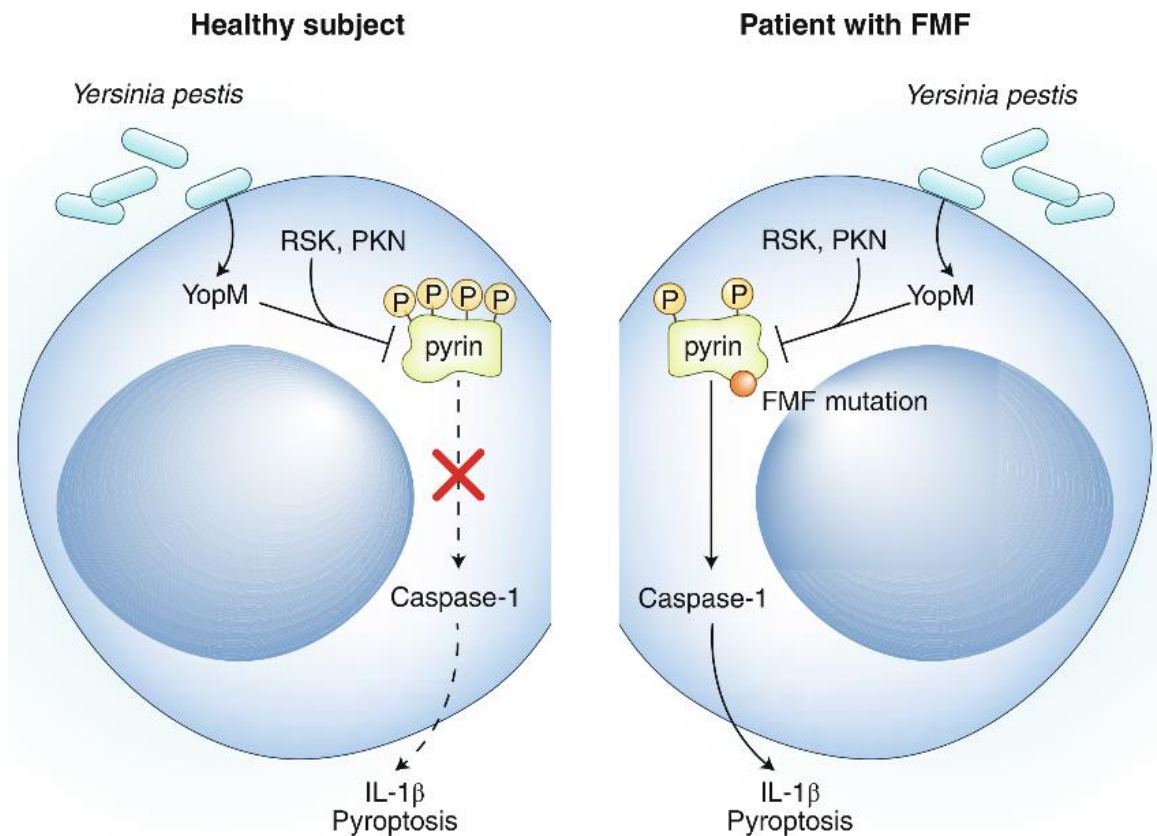


Fig. 1: Pyrin mutations causing Familial Mediterranean fever are associated with increased release of pro-inflammatory cytokines upon *Yersinia pestis* infection

Upon *Yersinia pestis* infection, the virulence factor YopM inhibits the IL-1 β -dependent host response by recruiting host RSK and PKN protein kinases. RSKs and PKN negatively regulate the pyrin inflammasome by phosphorylation. In FMF patients, pyrin mutations attenuate YopM-induced inhibition, resulting in increased release of the pro-inflammatory IL-1 β cytokine.