Glatter KA, et al., J Clin Immunol Immunother 2020, 6: 051
DOI: 10.24966/CIIT-8844/1000051

HSOA Journal of Clinical Immunology and Immunotherapy

Review Article

Immunologic Aspects of Plague Immunity and Familial Mediterranean Fever

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Abstract

The bubonic plague killed over 25 million people or greater than one-third of Europe's population during the fourteenth century. Its causative agent is *Yersinia pestis*, a gram-negative bacterium which continues to cause plague deaths in modern times and can be used as a weapon of mass destruction. Present-day Israeli Jews carry the recessive familial Mediterranean fever (FMF) at high rates, suggesting that their ancestors carried the mutation at similarly high rates, perhaps because it confers a protective advantage to carriers. FMF carriers possess a gain-in-function in pyrin, an important component in assembling inflammasomes, which fight infections and cancer. *Yersinia pestis* reduces production of IL-1β and IL-18, allowing the infection to spread quickly, usually leading to death in untreated hosts. FMF carriers possess immunity to plague infection, which we speculate in our recent *American Journal of Medicine* manuscript on this topic that this allowed fourteenth century European Jews to survive the plague at much higher rates than Christians, contributing to anti-Semitic violence during this period. We recommend that Israel add FMF screening to their national genetic screening program and that greater research be done to investigate if this gain-of-function in pyrin seen with FMF could provide immunity against other infections and as a potential cancer fighting agent.

Keywords: Bubonic plague; Familial mediterranean fever; Pyrin; Inflammasome; Evolutionary adaptation; *Yersinia pestis*

Introduction

The SARS-CoV-2 or novel coronavirus has infected millions and killed over 1.5 million people worldwide, yet it pales in comparison to the "Black Death" or bubonic plague during the fourteenth century caused by the bacterium *Yersinia pestis* [1,2]. Although today effective antibiotic treatments are available for the plague, occasional plague outbreaks still occur in modern times including in California and Mongolia [3,4]. *Yersinia pestis* has been labeled as a potential weapon of mass destruction for use with bioterrorism [5]. Our recent publication in the *American Journal of Medicine* entitled "History of the Plague: An Ancient Pandemic for the Age of Covid-19" proposes a novel theory that fourteenth century European Jews carried the familial Mediterranean fever (FMF) mutation, which rendered them immune from contracting the plague and thus died at lower rates than Christians from the disease [6]. FMF mutations confer a gain-of-function in pyrin, a major immune regulator by promoting assembly of inflammasomes and amplification of the immune system to fight infections and cancer [7]. This Current Opinion article reviews the historical and clinical features of the bubonic plague and describes the immunological aspects of its molecular background. Such findings may stimulate discussion in the larger immunology community and spur research efforts at exploring potential infection and cancer fighting modalities within this FMF-pyrin connection.

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Citation: Glatter KA, Finkelman P (2020) Immunologic Aspects of Plague Immunity and Familial Mediterranean Fever. J Clin Immunol Immunother 6: 051.

Received: December 15, 2020; **Accepted:** December 24, 2020; **Published:** December 31, 2020

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The Black Death or Bubonic Plague

At least one-third of Europe's population or over 25 million people in the 14th century died from the Black Death, which stands as one of the worst pandemics in human history [2,8,9]. The plague appears to be an ancient disease. Bronze Age skeletons show evidence of plague deaths as early as 3,000 BCE [10]. The Justinian Plague in 541 CE was one of the first, large recorded bubonic plague outbreaks and affected the entire Mediterranean basin and parts of Africa [8-10]. The bubonic plague arrived in Sicily in October 1347 via ship and spread rapidly across Europe over the next few years. The plague receded and resurfaced across the continent for several centuries. In 1894, Alexandre Yersin (and independently by Shibasaburo Kitasato) identified *Yersinia pestis*, a gram-negative rod bacterium of the species *Enterobacteriaceae*, as the plague's causative agent [2,8-10]. Its primary vector for transmission was a flea, *Xenopsylla cheopis*, initially carried by the black rat or *Rattus rattus*. Infected fleas were transported by rats, other rodents, and humans over long distances but could also infest grain and clothing. Newer data suggest that human body lice with some direct human-to-human transmission may also have played a role in the plague's spread [11].

Christians thought the plague was a punishment from God and obviously had no clear understanding of its bacterial origins. Europe's tiny Jewish minority was quickly accused of spreading the Black Death by poisoning the wells and the water supply, although anti-Jewish sentiment clearly had predated the plague [8-12]. Over the next few years, tens of thousands of Jews were murdered, often burned alive or tortured, and at least 235 Jewish communities experienced mass persecution [12].

Clinical Plague Manifestations

There are three major clinical forms of the plague [13,14]. In the most common bubonic plague type, bacteria from an infected flea

bite migrate to regional lymph nodes and multiply after an average incubation period of two to eight days. Sudden onset of high fevers and painful buboes (swellings) in the axillary, groin, and cervical regions lead to death quickly in most untreated patients. The septicemic plague form occurs when the bacteria multiply in the blood, often causing disseminated intravascular coagulation and gangrene of the extremities. Finally, the rare pneumonic plague subtype is spread by inhalation of infected aerosolized droplets (as with coronavirus transmission), leading rapidly to hemoptysis and death [13,14]. The latter two types are invariably fatal without treatment. Early recognition and treatment with streptomycin (or gentamycin) or a combination of doxycycline, chloramphenicol and ciprofloxacin can cure the bubonic plague [13,14].

Familial Mediterranean Fever and Pyrin

Familial Mediterranean Fever (FMF) is a rare, recessive disease mainly seen in people of Armenian, Arab, Jewish, or Turkish ancestry [15,16]. Symptoms include arthritis, fevers, and abdominal pain and last 12-72 hours, with most patients presenting by age 20 [15,16]. Those affected are generally completely normal between episodes. In 1997, the FMF *MEFV* gene was identified from an international patient cohort [17]. Over 310 FMF mutations have been identified on the short arm of chromosome 16, at 16p13.3 [15]. The protein product of *MEFV* is termed "pyrin," from the Greek word for "fever." The *MEFV* gene contains 781 codons and 10 exons [15-17]. Pyrin is an extremely important and versatile immune regulator which fights infection and cancer. At least nine pathogenic mutations have been described in the FMF gene including M680I, M694V, M694I, V726A, R761H, A744S, I692del, E167D, and T267I [15-18].

Inflammasomes were only discovered in 2002 and are the immune platforms which form in the cell cytosol upon sensing invasive pathogens [19]. Pyrin is a cytosolic pattern-recognition receptor (PRR) which is expressed in monocytes, activated macrophages, and neutrophils when pathogen/danger-associated molecular patterns (PAMPs/DAMPs) are detected [7,19]. Once activated, pyrin assembles inflammasomes, leading to activation of caspase-1, a cysteine proteinase [19-22]. Caspase-1, in turn, converts pro-IL-1β and pro-IL-18 into their mature cytokine forms (IL-1β and IL-18). Caspase-1 cleaves GSDMD, the pore-forming protein gasdermin D (GSDMD), which is involved with pyroptosis or cell death when a macrophage infected with a pathogen kills itself (19-22). Broadly speaking, IL-1β is a fever-causing cytokine produced by activated macrophages [23]. IL-18 amplifies the immune response by inducing other inflammatory cytokines like IL-4, IL-8, and IL-13 and produces IFN-γ [24,25]. IL-18 also enhances the cytotoxic activity of CD8, cytotoxic T cells, and natural killer (NK) cells through upregulation of FasL [24,25]. Thus, pyrin is a critical molecule in the immune system's vast and complex amplification process to fight infection through these intricate and interrelated mechanisms.

Using a Trojan-horse type of strategy, *Yersinia pestis* enters host cells through a prototypical type III secretion system used by other gram-negative rod bacteria [7,18,26,27]. It has a broad range of sophisticated mechanisms to inactivate the body's immune system and quickly disseminate throughout the body. It has several "Yops" (Yersinia outer proteins) which wreak havoc on the invaded host [7,18,26,27]. YopE and YopT stop the body from killing cells infected with *Yersinia pestis* by shutting off RhoA GTPases. YopM inhibits caspase-1 and blocks the pyrin inflammasome [7,18,26-28]. *Yersinia pestis* reduces production of IL-1β and IL-18, blocking the immune system from mounting a robust immune response [7,18,26-28]. The bacteria shut off natural immune defenses and thus can overwhelm its human host easily, leading to death.

Patients who carry the FMF mutation have a "gain-of-function" in the pyrin gene. Pyrin's activity is always "on." For infected subjects who lack the FMF mutation, *Yersinia pestis* shuts off pyrin [7,18,26-28]. Molecular studies using pyrin knock-out mice demonstrate that lacking pyrin increases susceptibility to the plague infection, while having a superabundance of pyrin (which FMF mutation carriers have) dramatically increases resistance to the plague [7,18,26-28]. The mutation confers natural resistance or immunity to the plague, enabling higher survival rates [7,18, 26-28]. Similar to carrying the sickle cell trait and having resistance to malaria, those harboring the FMF mutation are resistant to contracting the plague. Another benefit seen from the FMF mutation (either as an FMF patient or as an FMF carrier) appears to be a reduced cancer rate, although its precise mechanism is unclear [29,30]. Very little has been described in this growing area of research, namely the lower cancer rates evident among FMF patients. One publication from Israel found a markedly diminished incidence of malignancy among 8,534 Israeli FMF patients compared with matched, non-FMF controls, a finding that was reproduced in the Turkish FMF literature [29,30]. Such reports support the concept that the immune system fights both infection and cancer [31,32]. Additionally, this represents a novel research area from which new cancer-fighting agents could potentially be developed, namely utilizing gain-of-function pyrin agents.

Evolutionary Adaptation with the FMF Mutation

Sickle cell disease demonstrates how a genetic mutation evolved over time to protect its host population from malaria. Annually, as many as four to six hundred million people worldwide contract malaria, with over one million deaths [33,34]. An infected female *Anopheles* mosquito transmits the *Plasmodium falciparum* parasite by biting its human host. A point mutation in the β-globin gene that produces hemoglobin generates sickle cell hemoglobin [33,34]. Carrying sickle cell trait renders the subject relatively resistant (although not completely) to contracting malaria, which provides a significant generational benefit. Sickle cell disease itself (with two copies of the mutated hemoglobin gene) is a serious medical condition which causes death in most untreated patients before age twenty [33,34]. Approximately 7-10% of the African American community in the United State have sickle cell trait [33,34]. Thus, a comparison may be drawn between carrying sickle cell trait and resistance to developing malaria with those harboring the familial Mediterranean fever mutation and not contracting the plague. However, in contrast, sickle cell disease represents a very lethal disease which shortens the affected patient's lifespan, whereas most cases of familial Mediterranean fever are mild and rarely lead to death [15].

Like sickle cell trait and resistance to malaria, those harboring the FMF mutation are relatively resistant to contracting the plague, as an important example of an evolutionary adaptation [6,18,19]. Between 20% and 40% of Israeli Jews carry a recessive mutation in the FMF gene [35-37]. This mutation is found throughout the Middle East, but at the time of the Black Death, Jews were the only large European community with Middle Eastern origins. We hypothesize that the

presence of the FMF mutation would have allowed fourteenth century European Jews to survive the plague at higher rates than their non-Jewish neighbors, which may have led European Christians to blame Jews for spreading the plague [6,9,38]. It is unknown if FMF carriers possess resistance to other common infections like pneumonia, sepsis, or even coronavirus. The genetic pressure upon carriers of FMF over the millennia selected out those individuals to survive the plague (and perhaps other infections) at much higher rates than non-FMF carriers, which is likely why this otherwise rare mutation has been enriched in this particular population.

Conclusions

The Black Death, caused by the bacterium *Yersinia pestis*, killed millions of Europeans during the 14th century (and beyond), but those who carry the familial Mediterranean fever (FMF) trait survived at higher rates due to a gain-of-function in pyrin [6,18,26]. Pyrin is a critical player in the production of inflammasomes, which helps fight infections like the plague and also cancer [7,19,32]. A surprisingly high percentage of present-day Israeli Jews carry FMF mutations [35-37]. This point argues for its evolutionary advantage in protecting carriers from contracting the bubonic plague [6,18,26]. This genetic factor was unknown in the 14th century and helped convince the larger European population that Jews caused the disease, contributing to the subsequent massacres against the Jews. Our recent publication on the history of the plague highlights how modern molecular techniques and genetic technology can provide scientific explanations for these historical events [6]. Additionally, several original ideas stem directly from our work. First, we recommend that Israel add FMF to its national genetic screening program of newborn infants and also when screening is done elsewhere for Jewish-associated genetic mutations. Currently, any mutation with an estimated frequency above 1:60 in the Israeli population is screened for at birth in Israel, but FMF is not currently included in this panel [39]. We propose that FMF should be incorporated into the Israeli genetic screening program. Second, FMF and protection from the plague represent another important medical example of an evolutionary genetic adaptation, similar to sickle cell and malaria [33,34]. The FMF carrier mutation is widespread among Jewish and other Middle Eastern populations, which suggests that its benefits may extend far beyond protection from the plague [35-37]. The pyrin gain-of-function's role in fighting other infections and cancer needs to be better defined and represents a critical area for future research endeavors [7,19,27]. Finally, studying the medical, molecular, and genetic aspects of the Black Death can lead to new research insights and highlights the important relationship between history and science.

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