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A HYPOTHETICAL ROLE FOR PLAGUE IN THE SELECTION OF *MEFV* MUTATION CARRIERS IN THE MEDITERRANEAN AREA

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Abstract
Familial Mediterranean fever (FMF) is the most common autoinflammatory disease associated with mutations in the *MEFV* gene encoding Pyrin. *MEFV* mutations are frequent in the Mediterranean region. Increased resistance to an infection endemic to this area could have caused a selective advantage for individuals with *MEFV* mutations. Recent studies have shown that Pyrin is a part of host defense against microorganisms and it gets activated after sensing Rho GTPase inactivation by bacteria such as *Clostridium difficile* or *Yersinia pestis*. However, *Yersinia species* have another effector molecule, YopM which inhibits Pyrin in addition to RhoA modifiers YopE and YopT. Continuously overactive Pyrin in individuals with *MEFV* mutations could be a good host defense against Yersinia infections. *Y. pestis* causes plague, which led to a devastating pandemic in the Mediterranean basin. Thus, plague could be the infection which caused a selective biologic advantage for *MEFV* mutation carriers in this area.

Keywords: Familial Mediterranean fever, Plague**,** Missense mutation, Hypothesis
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Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease characterized by recurrent attacks of fever and serosa inflammation [1,2]. It is associated with mutations in the *MEFV* gene, which encodes Pyrin [3].*MEFV* mutations are frequent in the Mediterranean basin [4]. The carrier frequency is around 1/5 among Ashkenazi Jews, 1/5 among Turks, and 1/7 among Armenians [5,6,7]. Although it is considered an autosomal recessive disease, heterozygotes may also express the phenotype [4]. The mainstay of FMF treatment is colchicine which suppresses subclinical inflammation and prevents attacks in most patients [1]. Anti-interleukin 1 drugs

are used in colchicine-resistant or colchicine-intolerant patients [1].

Evolution of the human genome has been affected by infectious diseases. Especially infections that cause epidemics/pandemics with high mortality could have significant effects on genome evolution through selective biologic advantage. Thus, it has been an appealing hypothesis that increased resistance to an infectious agent endemic to the Mediterranean area caused a selective advantage for *MEFV* heterozygotes. Previously, two alternative hypotheses have been put forward as tuberculosis and brucellosis being candidate infections that might have caused the selection of individuals with *MEFV* mutations in the Mediterranean basin [8,9].
Based on the epidemiologic data of lower mortality from tuberculosis among Tunis Jews compared to the French living in the same area, Cattan et al. [8] hypothesized that lower severity of tuberculosis or decreased mortality from tuberculosis might have provided an advantage to *MEFV* carriers in the area. In a study testing the hypothesis of tuberculosis being the infection causing selection of *MEFV* heterozygotes, Ozen et al. [10] demonstrated that there was no statistically significant difference in *MEFV* variant carrier frequency between tuberculosis patients and healthy controls.
Ross et al. [9] hypothesized that *MEFV* mutations might have been protective against intracellular microorganisms such as *Brucella mellitensis* since these mutations cause a pro-inflammatory state with high levels of interferon-gamma. Brucellosis is still endemic in Middle East area because of the reliance for meat and dairy products of goats and ships which are the main reservoirs for the disease [9]. This hypothesis has never been tested in a case-control study comparing the frequency of *MEFV* mutations between brucellosis patients and healthy controls.

It is not possible to disprove previous hypotheses on tuberculosis and brucellosis. However, recent advances in our understanding of FMF pathogenesis, including Rho GTPases, Pyrin, and pathogen interactions have paved the way for a new hypothesis.

RhoA activates serine-threonine kinases PKN1 and PKN2, which phosphorylates serine residues of human Pyrin at positions 208 and 242 [11]. Phosphopyrin binds to 14-3-3 proteins that inhibit inflammasome activation [11]. Several microorganisms such as *Clostridium difficile*, *Clostridium botulinum*, and *Burkholderia cenocepacia* modify Rho GTPases in order to disable host cell cytoskeletal organization and associated host defense mechanisms such as phagocytosis and leukocyte migration [11.12]. On the other hand, as a counter-reaction from the host, Pyrin senses Rho modification by microorganisms and gets activated through the mechanism mentioned above (lack of inhibition by RhoA). However, some pathogens like *Yersinia pestis* and *Yersinia pseudotuberculosis* are one step ahead with their clever strategy.

While bacterial effectors of YopE and YopT of *Yersinia* species modify and inactivate Rho GTPases; Pyrin activation in response to RhoA inactivation is counteracted by another effector of *Yersinia*, YopM which causes inhibition of Pyrin [13,14]. Knock-in mice studies strongly suggest that *MEFV* mutations in FMF are “gain-of-function” mutation causing an overactive Pyrin inducing inflammasome formation and IL-1β production [15]. This continuously active Pyrin could be a good host defense against bacteria like *Yersinia pestis*.
Yersinia pestis causes a flea-borne zoonosis called plague [16]. It caused a devastating pandemic,called the Justinian Plague, in 542 AD in the Mediterranean basin, which is estimated to have caused 100 million deaths [17]. Plague usually starts with nonspecific symptoms similar to flulike high fever and malaise [18]. It has different clinical forms such as bubonic (with swelling in the regional lymph nodes and dry, red, hot skin), pneumonic (with severe cough and chest X-ray findings), and septicemic (sudden high fever and chills) [18]. It usually causes skin lesions in the form of carbuncles (deep ulcers encased by dark scabs) [19].

Yersinia species have been evolved to overcome host defense, including activated Pyrin inflammasome in response to Rho inhibition. Also, the human host might have been evolved to counter-act by keeping the Pyrin inflammasome overactive constantly, which is the case in *MEFV* mutation carriers. Thus, plague could be a strong candidate for an infection causing selective biologic

advantage for *MEFV* mutation carriers in the Mediterranean basin. This presented hypothesis could be tested by checking *MEFV* mutations in plague patients and healthy controls who live in the same area. However, the significant difference of *MEFV* mutation frequency could also appear between severe plague cases and patients with relatively milder infection.

It is important to emphasize two points. First, this hypothesis does not mean that FMF patients (or *MEFV* heterozygotes) are resistant to plague. Second, it is not acceptable to delay FMF treatment in areas where plague is endemic (such as areas in Africa or Asia) considering that the subclinical inflammation of FMF could be protective against this infection. In the modern era, we have effective antibiotics for treating *Y. pestis* infections. However, if left untreated, FMF could cause a significant complication, amyloidosis which is responsible for long-term morbidity and mortality in FMF [2]. Thus, this hypothesis could stimulate our thinking about FMF pathogenesis with possible links to infections, but it should not affect our clinical practice while evaluating/treating FMF patients or patients with plague.

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EDB designed the structure of the article, drafted and critically revised the text, and approved the final version of the manuscript.

CONFLICTS OF INTEREST
EDB declares that she has no conflict of interest.

DISCLAIMER
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Жерорта теңізі аймағындағы MEFV мутациясының тасымалдаушыларын таңдаудағы обаның гипотетикалық рөлі

Түйіндеме

Отбасылық Жерорта теңізінің безгегі (FMF) - бұл MEFV генінің пиринді кодтайтын мутацияларымен байланысты ең көп таралған ауто-қабыну ауруы. MEFV мутациясы Жерорта теңізі аймағында жиі кездеседі. Осы аймақтағы эндемиялық инфекцияға қарсы тұрақтылықтың жоғарылауы MEFV мутациясы бар адамдар үшін таңдаулы артықшылық болуы мүмкін. Жақында жүргізілген зерттеулер пириннің микроорганизмдерден қорғану бөлігі болып табылады және Clostridium difficile немесе Yersinia pestis сияқты бактериялардың Rho GTPase инактивациясынан кейін белсенді болады. Алайда, Yersinia түрлерінде RhoAmodifiersYopE және YopT-ға қосымша пиринді тежейтін тағы бір эффекторлы молекула бар - YopM. MEFV мутациясы бар адамдардағы үнемі байқалатын шамадан тыс белсенді пирин Yersinia инфекцияларынан жақсы қорғаныс болуы мүмкін. Y. pestis Жерорта теңізі бассейнінде жойқын пандемияға алып келген обаны тудырушы. Осылайша, оба осы аймақтағы MEFV мутациясының тасымалдаушылары үшін таңдамалы биологиялық артықшылықты тудыратын инфекция болуы мүмкін.

Түйін сөздер: Орталық Азия, тақырып ретінде мерзімді басылымдар, гипотеза, зерттеу дизайны

Дәйексөз үшін: Бату Е. Жерорта теңізі аймағындағы MEFV мутациясының тасымалдаушыларын таңдаудағы обаның гипотетикалық рөлі. Медициналық гепотиза мен этиканың Орта Азиялық журналы. – 2020. – №1 (1). – Б. 55 - 59. https://doi.org/10.47316/cajmhe.2020.1.1.07

Гипотетическая роль чумы в селекции носителей мутации MEFV в районе Средиземноморья

Резюме

Семейная средиземноморская лихорадка (ССЛ) является наиболее распространенным ауто-воспалительным заболеванием, связанным с мутациями в гене MEFV, который кодирует пирин. MEFV мутации часто встречаются в средиземноморском регионе. Повышенная устойчивость к заболеванию, эндемичному для этой области, могла бы стать селективным

преимуществом людей с мутациями MEFV. Недавние исследования показали, что пирин является частью защиты хозяина от микроорганизмов и активируется после инактивации Rho GTPase бактериями, такими как *Clostridium difficile* или *Yersinia pestis*. Однако *Yersinia species* имеет другую эффекторную молекулу, YopM, которая ингибирует пирин в дополнение к модификаторам RhoA YopE и YopT. Непрерывно сверхактивный пирин может быть защитным фактором людей с мутациями MEFV хозяина от иерсиниозных инфекций. *Y. pestis* вызывает чуму, которая привела к разрушительной пандемии в бассейне Средиземного моря. Таким образом, чума могла быть инфекцией, которая стала причиной селективного биологического преимущества носителей мутации MEFV в этой области.

Ключевые слова: Центральная Азия, Периодика как тема, Гипотеза, дизайн исследования
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