2016

CASPASE-12, Rheumatoid Arthritis, and the Dog That Didn't Bark

Evan Hermel
Touro University California, evan.hermel@tu.edu

Immunogenetics: Open Access

Hermel, Immunogenet open access 2016, 1:1

Commentary Open Access

Caspase-12, Rheumatoid Arthritis, and the Dog that Didn't Bark

Evan Hermel*

Department of Basic Sciences, College of Osteopathic Medicine, Touro University-CA, USA

Corresponding author: Evan Hermel, Department of Basic Sciences, College of Osteopathic Medicine, Touro University-CA, USA; Tel: 707-638-5241; Fax: 707-638-5255; E-mail: evan.hermel@tu.edu

Received Date: January 21, 2016; **Accepted Date:** February 22, 2016; **Published Date:** February 29, 2016

Abstract

CASPASE-12 (CASP12) has an anti-inflammatory function during infection. To determine and if CASP12 could protect against inflammatory disease, we investigated the distribution of CASP12 alleles in African-Americans (AA) with rheumatoid arthritis (RA). CASP12 homozygous patients had lower baseline joint narrowing and total disease scores. However, there was no significant difference for distribution of CASP12 genotypes between AA controls and patients with RA, or any other clinical criteria for this disease. CASP12 homozygosity appears to be, at best a subtle protective factor for some aspects of RA in AA patients. This raises an intriguing issue as to how this protein would not have a more significant role in an inflammatory disease process.

Introduction

Most humans lack a functional CASP12 gene. A pseudogene (CASP12p1) resulting from a premature termination mutation [1] is found in all Caucasians and East Asians examined, and in 80% of people of African lineage [2,3]. In approximately 20% of persons of recent African descent, the pseudogene is rescued by a single nucleotide polymorphism (#rs497116; A→G) that converts the premature stop codon into a functional one encoding Arg [2,3].

This functional allele is a risk factor for sepsis in persons of African descent in response to pro-inflammatory mediators such as bacterial lipopolysaccharide. This is due to CASP12's ability to down-regulate production of inflammatory cytokines such as interleukin (IL)-1β or tumor necrosis factor (TNF) and by interfering with the activation of the transcription factor NFκb [4,5]. In individuals of African descent with severe sepsis, the mortality rate was 54% in individuals with the CASP12 allele, compared with 17% in individuals with only the CASP12p1 allele. Knockout mice lacking CASP12 are also less susceptible to sepsis and death than wild-type mice [6]. These anti-inflammatory activities are proposed to result from CASP12 biding to inflammasome components such as CASP1 and CASP5 [6] and/or to adaptor proteins downstream of pattern recognition molecules, such as NOD2 [7] or RIG-I [8].

The intact allele of CASP12 is still found in approximately 20% of African-Americans, with higher allele frequencies in some populations in sub-Saharan Africans, and in some populations of Central and South Asians [2,3,9]. This implies that despite its selective disadvantage, it may play a protective in inflammatory processes exploited by specific pathogens [10].

A corollary to the observation that CASP12 is a risk factor for sepsis would be that CASP12 is protective against some inflammatory autoimmune diseases. If CASP12 causes a derangement in IL-1β or TNF production, individuals carrying the CASP12 allele, but not CASP12p1, should be less likely to develop inflammatory disease. To test this hypothesis, we sought to determine if CASP12 genotype would have an effect upon the pathologic manifestations of rheumatoid arthritis (RA). We genotyped CASP12 in patients and controls from the Consortium for Longitudinal Evaluation of African-Americans with Early Rheumatoid Arthritis (CLEAR) and the Veterans Administration Rheumatoid Arthritis (VARA) Registry of African-Americans with RA [11,12].

CASP12 genotype was assessed for several diagnostic criteria for RA according to the 1987 American College of Rheumatology (ACR) RA classification criteria [13]. These include scored radiographic changes (joint erosion, joint space narrowing and their combined scores), presence of rheumatoid nodules or serum rheumatoid factor (RF), and the number of tender or swollen joints (out of 28) at baseline. In addition, we compared genotype to serologic criteria from the 2010 ACR/EULAR classification [14] for elevated C-reactive protein levels, elevated erythrocyte sedimentation rate, and presence of anti-citrullinated peptide antibodies (anti-CCP).

Our data found that frequencies of CASP12 alleles in both patients and controls were similar to normal controls reported by others [4,15]. There were no significant differences in the genotype and allele frequency between controls and RA patients, nor did genotype affect seropositivity of RF or anti-CCP. As expected, while nearly 20% of the controls were positive for RF, and only 3% were so for anti-CCP, and there was no connection to CASP12 genotype.

While possession of intact CASP12 had no overall effect upon the development of RA in AA, there was a subtle protective effect against the erosive pathologies of RA, as defined by radiographic changes of baseline joint erosion and joint space narrowing scores. Baseline joint narrowing and total disease scores were greater in those patients who were homozygous for the CASP12p1 pseudogene than those who were CASP12 homozygous. Joint erosion scores also appeared to be greater in CASP12p1 homozygotes, although not reaching statistical significance. No significant differences were found for any other clinical parameters.

Two questions arise from these findings. The first is how do the joint pathologies in RA arise? The second is what role does CASP12 play in autoimmune pathogenesis, if any?

The pathology of RA is mediated by chronic joint inflammation and synovial hyperplasia that ultimately lead to cartilage degradation and

bone destruction [16,17]. The major cellular effectors of these events CD4+ Th17 cells, which drive the process by the secretion of inflammatory cytokines either directly or indirectly from inflammatory cells [18-20]. Given the role of IL-1β and TNF in the pathogenesis of RA [18,21], the findings hint at pathways involved in the severity of joint damage, and open the possibility of identifying novel biomarkers for RA severity and disease progression, which, to date, are relatively few [22].

It is unknown how CASP12 exerts the protective effects described above. If CASP12 is indeed down regulatory, it may fail to reduce serum concentrations of IL-1β or other pathogenic cytokines below disease-inducing levels, but does so at the tissue or cellular level. This notion is supported by the observation that there is less macrophage infiltration into adipose tissues of obese African-American children who are CASP12-positive [23].

The key question emerging is CASP12 actually anti-inflammatory? Our own findings bring to mind "the dog that didn't bark". In the classic Sir Arthur Conan Doyle tale The Adventure of the Silver Blaze, Sherlock Holmes noted that the guard dog was supposed to bark at prowlers in the night, yet didn't do so prior to the occurrence of a crime [24]. And so human CASP12 is posited to downregulate inflammation mediated by cytokines, to such an extent that this activity renders a subject more susceptible to sepsis. This would explain the near extirpation of the functional allele from the vast majority of the human population [2,3].

Saleh and colleagues extended their finding on CASP12 and IL1-β to other inflammatory cytokines with the observation that in obese African-American children who are CASP12-positive have lower serum IL6 and C-reactive protein levels [23]. Unfortunately, these workers did not report on any findings concerning IL-1β or TNF; perhaps IL-1β is not triggered at a systemic level following metabolism-based inflammation, but IL-1β is activated by non-CASP1-mediated mechanisms in different disease states [21] or IL-1β production is not affected by CASP12. We lean toward the latter interpretation.

CASP12 genotype does not influence susceptibility or adverse events in African-Americans or black South Africans with community-acquired pneumonia [15]. In addition, susceptibility to Candida sepsis in Africans is not affected by CASP12 genotype, nor does it have any effect on serum inflammatory cytokine concentrations in the pathology of candidiasis [23] or in in vitro responses to Yersinia pestis [25]. While malaria would be an obvious candidate for a positive selective effect upon maintenance of CASP12, there is no association between CASP12 genotype and either the presentation of severe malaria or outcomes in individual clinical parameters in malaria patients [26].

CASP12's effects upon TNF production, which is elevated in all lupus patients, especially African-Americans [27], is also contradictory [5,25,28]. Further, while hepatitis C virus is an IL-1β inducer [29] CASP12 genotype has no effect in the clearance of this pathogen [30]. Confounding the metabolic findings described above by Skeldon and co-workers, no protective effects are found in African-American adults with CASP12 when metabolic parameters or C-reactive protein levels were assessed [23].

When we examined another inflammatory autoimmune disease in African-Americans, systemic lupus erythematosus (SLE), we found that CASP12 genotype was neither a risk factor nor protective. CASP12 polymorphisms did not affect any of the 11 ACR classification criteria, nor did our data demonstrate that CASP12 genotype had a significant effect upon serum IL-1β levels in an initial screen of sera from 14 patients. At best, we found a weak protective effect against the development of anti-double-stranded DNA antibodies, but no other autoantibodies (T. Fuchs, J.A. Kelly, E. Simon, K.L. Sivils and E. Hermel; in press, Immunology Lett.). It is also worth noting that in transgenic mice carrying human CASP12, the gene is downregulated in female mice, due to an endogenous estrogen response element [5]. This might explain why 90% of AA SLE patients are female [31] but is confounded by the observation that African-American male lupus patients have a more severe phenotype and worse outcomes [32,33].

While different findings for CASP12 effects (or lack thereof) described here may be due to sample size, populations tested, underlying disease states assessed, or the assay systems used, using CASP12 genotype to predict protection in rheumatic diseases, or even in infectious disease outcomes, appears to be problematic.

Acknowledgements

We are grateful to Dr. Denene Lofland for her careful proof-reading of this manuscript. This project was supported by an intramural grant from Touro University-California, and stipends from the Touro University California-College of Osteopathic Medicine's Master of Science Program in Medical Health Sciences. Dr Alejandro Gugliucci is also thanked for his long-time support.

References

1. Fischer H, Koenig U, Eckhart L, Tschachler E (2002) Human caspase 12 has acquired deleterious mutations. Biochem Biophys Res Commun 293: 722-726.
2. Kachapati K, O'Brien TR, Bergeron J, Zhang M, Dean M (2006) Population distribution of the functional caspase-12 allele. Hum Mutat 27: 975.
3. Xue Y, Daly A, Yngvadottir B, Liu M, Coop G, et al. (2006) Spread of an inactive form of caspase-12 in humans is due to recent positive selection. Am J Hum Genet 78: 659-670.
4. Saleh M, Vaillancourt JP, Graham RK, Huyck M, Srinivasula SM, et al. (2004) Differential modulation of endotoxin responsiveness by human caspase-12 polymorphisms. Nature 429: 75-79.
5. Yeretssian G, Doiron K, Shao W, Leavitt BR, Hayden MR, et al. (2009) Gender differences in expression of the human caspase-12 long variant determines susceptibility to Listeria monocytogenes infection. Proceedings of the National Academy of Sciences of the United States of America 106: 9016-9020.
6. Saleh M, Mathison JC, Wolinski MK, Bensinger SJ, Fitzgerald P, et al. (2006) Enhanced bacterial clearance and sepsis resistance in caspase-12-deficient mice. Nature 440: 1064-1068.
7. LeBlanc PM, Yeretssian G, Rutherford N, Doiron K, Nadiri A, et al. (2008) Caspase-12 modulates NOD signaling and regulates antimicrobial peptide production and mucosal immunity. Cell Host Microbe 3: 146-157.
8. Wang SH, Shih YL, Lee CC, Chen WL, Lin CJ, et al. (2009) The role of endoplasmic reticulum in cadmium-induced mesangial cell apoptosis. Chem Biol Interact 181: 45-51.
9. Yavari M, Brinkley G, Klapstein KD, Hartwig WC, Rao R, et al. (2012) Presence of the functional CASPASE-12 allele in Indian subpopulations. Int J Immunogenet 39: 389-393.
10. Hermel E, Klapstein KD (2011) A possible mechanism for maintenance of the deleterious allele of human CASPASE-12. Med Hypotheses 77: 803-806.

11. Bridges SL Jr, Hughes LB, Mikuls TR, Howard G, Tiwari HK, et al. (2003) Early rheumatoid arthritis in African-Americans: the CLEAR Registry. Clin Exp Rheumatol 21: S138-145.
12. Mikuls TR, Kazi S, Cipher D, Hooker R, Kerr GS, et al. (2007) The association of race and ethnicity with disease expression in male US veterans with rheumatoid arthritis. J Rheumatol 34: 1480-1484.
13. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31: 315-324.
14. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, et al. (2010) Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 62: 2569-2581.
15. Chen J, Wilson ES, Dahmer MK, Quasney MW, Waterer GW, et al. (2014) Lack of association of the caspase-12 long allele with community-acquired pneumonia in people of African descent. PLoS One 9: e89194.
16. Komatsu N, Takayanagi H (2012) Autoimmune arthritis: the interface between the immune system and joint. Adv Immunol 115: 45-71.
17. McInnes IB, Schett G (2011) The pathogenesis of rheumatoid arthritis.N Engl J Med 365: 2205-2219.
18. McInnes IB, Buckley CD, Isaacs JD, et al. (2016) Cytokines in rheumatoid arthritis - shaping the immunological landscape. Nat Rev Rheumatol 12: 63-68.
19. Brzustewicz E, Bryl E (2015) The role of cytokines in the pathogenesis of rheumatoid arthritis--Practical and potential application of cytokines as biomarkers and targets of personalized therapy. Cytokine 76: 527-536.
20. Furst DE and Emery P (2014) Rheumatoid arthritis pathophysiology: update on emerging cytokine and cytokine-associated cell targets. Rheumatology (Oxford) 53: 1560-1569.
21. Dinarello CA (2011) Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. Blood 117: 3720-3732.
22. Krabben A, Huizinga TW, Mil AH (2015) Biomarkers for radiographic progression in rheumatoid arthritis. Curr Pharm Des 21: 147-169.
23. Skeldon AM, Morizot A, Douglas T, Santoro N, Kursawe R, et al. (2016) Caspase-12, but Not Caspase-11, Inhibits Obesity and Insulin Resistan. J Immunol 196: 437-447.
24. Rosentul DC, Plantinga TS, Scott WK, Alexander BD, van de Geer NM, et al. (2012) The impact of caspase-12 on susceptibility to candidemia. Eur J Clin Microbiol Infect Dis 31: 277-280.
25. Ferwerda B, McCall MB, de Vries MC, Hopman J, Maiga B, et al. (2009) Caspase-12 and the inflammatory response to Yersinia pestis. PLoS One 4: e6870.
26. McCall MB, Ferwerda B, Hopman J, Ploemen I, Maiga B, et al. (2010) Persistence of full-length caspase-12 and its relation to malaria in West and Central African populations. European cytokine network 21: 77-83.
27. Weckerle CE, Mangale D, Franek BS, Kelly JA, Kumabe M, et al. (2012) Large-scale analysis of tumor necrosis factor alpha levels in systemic lupus erythematosus. Arthritis Rheum 64: 2947-2952.
28. Plantinga TS, Hamza OJ, Willment JA, Ferwerda B, van de Geer NM, et al. (2010) Genetic variation of innate immune genes in HIV-infected african patients with or without oropharyngeal candidiasis. J Acquir Immune Defic Syndr 55: 87-94.
29. Burdette D, Haskett A, Presser L, McRae S, Iqbal J, et al. (2012) Hepatitis C virus activates interleukin-1 via caspase-1-inflammasome complex. J Gen Virol 93: 235-246.
30. O'Brien TR, Kachapati K, Zhang M, Bergeron J, Edlin BR, et al. (2007) HCV infection clearance with functional or non-functional caspase-12. Scand J Gastroenterol 42: 416-417.
31. Feldman CH, Hiraki LT, Liu J, Fischer MA, Solomon DH, et al. (2013) Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000-2004. Arthritis Rheum 65: 753-763.
32. Campbell R Jr, Cooper GS, Gilkeson GS (2008) Two aspects of the clinical and humanistic burden of systemic lupus erythematosus: mortality risk and quality of life early in the course of disease. Arthritis Rheum 59: 458-464.
33. Ippolito A, Petri M (2008) An update on mortality in systemic lupus erythematosus. Clin Exp Rheumatol 26: S72-79.