Journal of Immunology 2017 vol.199 N10, pages 3604-3613

Macrophage-specific expression of IL-37 in hyperlipidemic mice attenuates atherosclerosis

McCurdy S., Baumer Y., Toulmin E., Lee B., Boisvert W.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

Copyright © 2017 by The American Association of Immunologists, Inc. inflammation, as well as the formation of lipid-laden macrophage foam cells within the vessel wall. IL-37 is recognized as an important anti-inflammatory cytokine expressed especially by immune cells. This study was undertaken to elucidate the role of macrophage-expressed IL-37 in reducing the production and effects of proinflammatory cytokines, preventing foam cell formation, and reducing the development of atherosclerosis. Expression of human IL-37 was achieved with a macrophage-specific overexpression system, using the CD68 promoter in mouse primary bone marrow-derived macrophages via retroviral transduction. Macrophage IL-37 expression in vitro resulted in decreased mRNA (e.g., IL-1B, IL-6, and IL-12) and secreted protein production (e.g., IL-6, M-CSF, and ICAM-1) of key inflammatory mediators. IL-37 expression also inhibited macrophage proliferation, apoptosis, and transmigration, as well as reduced lipid uptake, compared with controls in vitro. The in vivo effects of macrophage-expressed IL-37 were investigated through bone marrow transplantation of transduced hematopoietic stem cells into irradiated atherosclerosis-prone Ldlr2/2 mice. After 10 wk on a high-fat/high-cholesterol diet, mice with IL-37-expressing macrophages showed reduced disease pathogenesis, which was demonstrated by significantly less arterial plaque development and systemic inflammation compared with control mice. The athero-protective effect of macrophage-expressed IL-37 has implications for development of future therapies to treat atherosclerosis, as well as other chronic inflammatory diseases.

http://dx.doi.org/10.4049/jimmunol.1601907

References

[1] Moore, K. J., and I. Tabas. 2011. Macrophages in the pathogenesis of atherosclerosis. Cell 145: 341-355.

[2] Kunjathoor, V. V., M. Febbraio, E. A. Podrez, K. J. Moore, L. Andersson, S. Koehn, J. S. Rhee, R. Silverstein, H. F. Hoff, and M. W. Freeman. 2002. Scavenger receptors class A-I/II and CD36 are the principal receptors responsible for the uptake of modified low density lipoprotein leading to lipid loading in macrophages. J. Biol. Chem. 277: 49982-49988.

[3] Kruth, H. S. 2013. Fluid-phase pinocytosis of LDL by macrophages: A novel target to reduce macrophage cholesterol accumulation in atherosclerotic lesions. Curr. Pharm. Des. 19: 5865-5872.

[4] Shalhoub, J., M. A. Falck-Hansen, A. H. Davies, and C. Monaco. 2011. Innate immunity and monocyte-macrophage activation in atherosclerosis. J. Inflamm. 8: 9.

[5] Michael, D. R., T. G. Ashlin, C. S. Davies, H. Gallagher, T. W. Stoneman, M. L. Buckley, and D. P. Ramji. 2013. Differential regulation of macropinocytosis in macrophages by cytokines: implications for foam cell formation and atherosclerosis. Cytokine 64: 357-361.

[6] Kumar, S., P. C. McDonnell, R. Lehr, L. Tierney, M. N. Tzimas, D. E. Griswold, E. A. Capper, R. Tal-Singer, G. I. Wells, M. L. Doyle, and P. R. Young. 2000. Identification and initial characterization of four novel members of the interleukin-1 family. J. Biol. Chem. 275: 10308-10314.

[7] Boraschi, D., D. Lucchesi, S. Hainzl, M. Leitner, E. Maier, D. Mangelberger, G. J. Oostingh, T. Pfaller, C. Pixner, G. Posselt, et al. 2011. IL-37: A new antiinflammatory cytokine of the IL-1 family. Eur. Cytokine Netw. 22: 127-147.

[8] Bufler, P., F. Gamboni-Robertson, T. Azam, S. H. Kim, and C. A. Dinarello. 2004. Interleukin-1 homologues IL-1F7b and IL-18 contain functional mRNA instability elements within the coding region responsive to lipopolysaccharide. Biochem. J. 381: 503-510.

[9] Nold, M. F., C. A. Nold-Petry, J. A. Zepp, B. E. Palmer, P. Bufler, and C. A. Dinarello. 2010. IL-37 is a fundamental inhibitor of innate immunity. Nat. Immunol. 11: 1014-1022.

[10] Teng, X., Z. Hu, X. Wei, Z. Wang, T. Guan, N. Liu, X. Liu, N. Ye, G. Deng, C. Luo, et al. 2014. IL-37 ameliorates the inflammatory process in psoriasis by suppressing proinflammatory cytokine production. J. Immunol. 192: 1815-1823.

[11] Zhao, P. W., W. G. Jiang, L. Wang, Z. Y. Jiang, Y. X. Shan, and Y. F. Jiang. 2014. Plasma levels of IL-37 and correlation with TNF-A, IL-17A, and disease activity during DMARD treatment of rheumatoid arthritis. PLoS One 9: e95346.

[12] Ye, L., L. Ji, Z. Wen, Y. Zhou, D. Hu, Y. Li, T. Yu, B. Chen, J. Zhang, L. Ding, et al. 2014. IL-37 inhibits the production of inflammatory cytokines in peripheral blood mononuclear cells of patients with systemic lupus erythematosus: its correlation with disease activity. J. Transl. Med. 12: 69.

[13] Imaeda, H., K. Takahashi, T. Fujimoto, E. Kasumi, H. Ban, S. Bamba, H. Sonoda, T. Shimizu, Y. Fujiyama, and A. Andoh. 2013. Epithelial expression of interleukin-37b in inflammatory bowel disease. Clin. Exp. Immunol. 172: 410-416.

[14] Weidlich, S., A. M. Bulau, T. Schwerd, J. Althans, R. Kappler, S. Koletzko, D. Mayr, and P. Bufler. 2014. Intestinal expression of the anti-inflammatory interleukin-1 homologue IL-37 in pediatric inflammatory bowel disease. J. Pediatr. Gastroenterol. Nutr. 59: e18-e26.

[15] Højen, J. F., T. A. Rasmussen, K. L. Andersen, A. A. Winckelmann, R. R. Laursen, J. D. Gunst, H. J. Møller, M. Fujita, L. Østergaard, O. S. Søgaard, et al. 2015. Interleukin-37 expression is increased in chronic HIV-1-infected individuals and is associated with inflammation and the size of the total viral reservoir. Mol. Med. 21: 337-345.

[16] Ji, Q., Q. Zeng, Y. Huang, Y. Shi, Y. Lin, Z. Lu, K. Meng, B. Wu, K. Yu, M. Chai, et al. 2014. Elevated plasma IL-37, IL-18, and IL-18BP concentrations in patients with acute coronary syndrome. Mediators Inflamm. 2014: 165742.

[17] Ballak, D. B., J. A. van Diepen, A. R. Moschen, H. J. Jansen, A. Hijmans, G. J. Groenhof, F. Leenders, P. Bufler, M. V. Boekschoten, M. Muller, et al. 2014. IL-37 protects against obesity-induced inflammation and insulin resistance. Nat. Commun. 5: 4711.

[18] Luo, Y., X. Cai, S. Liu, S. Wang, C. A. Nold-Petry, M. F. Nold, P. Bufler, D. Norris, C. A. Dinarello, and M. Fujita. 2014. Suppression of antigen-specific adaptive immunity by IL-37 via induction of tolerogenic dendritic cells. Proc. Natl. Acad. Sci. USA 111: 15178-15183.

[19] Gough, P. J., and E. W. Raines. 2003. Gene therapy of apolipoprotein E-deficient mice using a novel macrophage-specific retroviral vector. Blood 101: 485-491.

[20] Wu, B. W., Q. T. Zeng, K. Meng, and Q. W. Ji. 2013. The potential role of IL-37 in atherosclerosis. Pharmazie 68: 857-860.

[21] Chai, M., Q. Ji, H. Zhang, Y. Zhou, Q. Yang, Y. Zhou, G. Guo, W. Liu, W. Han, L. Yang, et al. 2015. The protective effect of interleukin-37 on vascular calcification and Atherosclerosis in apolipoprotein E-deficient mice with diabetes. J. Interferon Cytokine Res. 35: 530-539.

[22] Huang, J., F. L. Hou, A. Y. Zhang, and Z. L. Li. 2016. Protective effect of the polarity of macrophages regulated by IL-37 on atherosclerosis. Genet. Mol. Res. 15. Available at: http://www.funpecrp.com.br/gmr/year2016/vol15-2/pdf/gmr7616.pdf.

[23] Han, X., S. Kitamoto, H. Wang, and W. A. Boisvert. 2010. Interleukin-10 overexpression in macrophages suppresses atherosclerosis in hyperlipidemic mice. FASEB J. 24: 2869-2880.

[24] Dinarello, C. A. 2009. Immunological and inflammatory functions of the interleukin-1 family. Annu. Rev. Immunol. 27: 519-550.

[25] Biasucci, L. M., A. Vitelli, G. Liuzzo, S. Altamura, G. Caligiuri, C. Monaco, A. G. Rebuzzi, G. Ciliberto, and A. Maseri. 1996. Elevated levels of interleukin-6 in unstable angina. Circulation 94: 874-877.

[26] Kishimoto, T., S. Akira, M. Narazaki, and T. Taga. 1995. Interleukin-6 family of cytokines and gp130. Blood 86: 1243-1254.

[27] Sharaf, N., M. J. Nicklin, and F. S. di Giovine. 2014. Long-range DNA interactions at the IL-1/IL-36/IL-37 gene cluster (2q13) are induced by activation of monocytes. Cytokine 68: 16-22.

[28] Rosenfeld, M. E., S. Ylä-Herttuala, B. A. Lipton, V. A. Ord, J. L. Witztum, and D. Steinberg. 1992. Macrophage colony-stimulating factor mRNA and protein in atherosclerotic lesions of rabbits and humans. Am. J. Pathol. 140: 291-300.

[29] Clinton, S. K., R. Underwood, L. Hayes, M. L. Sherman, D. W. Kufe, and P. Libby. 1992. Macrophage colony-stimulating factor gene expression in vascular cells and in experimental and human atherosclerosis. Am. J. Pathol. 140: 301-316.

[30] Smith, J. D., E. Trogan, M. Ginsberg, C. Grigaux, J. Tian, and M. Miyata. 1995. Decreased atherosclerosis in mice deficient in both macrophage colonystimulating factor (op) and apolipoprotein E. Proc. Natl. Acad. Sci. USA 92: 8264-8268.

[31] Nold-Petry, C. A., C. Y. Lo, I. Rudloff, K. D. Elgass, S. Li, M. P. Gantier, A. S. Lotz-Havla, S. W. Gersting, S. X. Cho, J. C. Lao, et al. 2015. IL-37 requires the receptors IL-18Ra and IL-1R8 (SIGIRR) to carry out its multifaceted anti-inflammatory program upon innate signal transduction. Nat. Immunol. 16: 354-365.

[32] Robbins, C. S., I. Hilgendorf, G. F. Weber, I. Theurl, Y. Iwamoto, J. L. Figueiredo, R. Gorbatov, G. K. Sukhova, L. M. Gerhardt, D. Smyth, et al. 2013. Local proliferation dominates lesional macrophage accumulation in atherosclerosis. Nat. Med. 19: 1166-1172.

[33] Saraswathi, V., and A. H. Hasty. 2006. The role of lipolysis in mediating the proinflammatory effects of very low density lipoproteins in mouse peritoneal macrophages. J. Lipid Res. 47: 1406-1415.

[34] Bulau, A. M., M. F. Nold, S. Li, C. A. Nold-Petry, M. Fink, A. Mansell, T. Schwerd, J. Hong, A. Rubartelli, C. A. Dinarello, and P. Bufler. 2014. Role of caspase-1 in nuclear translocation of IL-37, release of the cytokine, and IL-37 inhibition of innate immune responses. Proc. Natl. Acad. Sci. USA 111: 2650-2655.

[35] Sharma, S., N. Kulk, M. F. Nold, R. Gräf, S. H. Kim, D. Reinhardt, C. A. Dinarello, and P. Bufler. 2008. The IL-1 family member 7b translocates to the nucleus and down-regulates proinflammatory cytokines. J. Immunol. 180: 5477-5482.