Bölüm 23

ATEROGENEZ VE İNFLAMASYON

Kenan ERDEM[1]

GİRİŞ

Ateroskleroz; koroner arter hastalığı, periferik arter hastalığı ve serebrovasküler hastalığın en yaygın altta yatan patolojisidir (1). Büyük ve orta büyüklükteki arterlerin subendotelyal intimal tabakasında zamanla oluşan plaklar, arter lümen çapının kan akımını azaltacak şekilde daralmasına ve kritik doku hipoksisine neden olur. Kardiyovasküler hastalıkların tanı ve tedavisindeki hızlı gelişmelere rağmen, bu hastalıklar tüm dünyada en önde gelen ölüm nedenleri arasındadır (2). Ülkemizde koroner kalp hastalığı ölüm nedenleri arasında birinci sırada gelmektedir. 1990-2008 yıllarını kapsayan TEKHARF çalışması göstermiştir ki; koroner kalp hastalığı kökenli ölümler erkeklerde 1000 kişi-yılında 7.64, kadınlarda 3.84 seviyelerindedir (3). Kardiyovasküler hastalıkların tanı ve tedavisindeki yüksek maliyet ülke ekonomileri açısından koroner arter hastalığının (KAH) önemini göstermektedir (4).

Ateroskleroz; athere Yunanca "bulamaç ve yulaf lapası" ve "skleros" yine Yunanca sertleşme anlamına gelen kelimeleri içerir (5). Aterojenik süreç endotelyal disfonksiyon bölgelerinde subendotelyal boşlukta plazma lipoproteinlerinin birikmesiyle başlar. Aterosklerozdaki ana lezyonlar zamanla aterosklerotik plak oluşumuna dönüşen düz kas hücresinin eşlik ettiği arter bölümlerinde lipid birikimi ve fibröz matrkis proliferasyonu ile karakterizedir (6).

[1] Dr. Öğr. Üyesi, Selçuk Üniversitesi Tıp Fakültesi Kardiyoloji AD, erdemkenebr@yahoo.com

bisyonu hiperkolesterolemik tavşanlarda neointimal kalınlaşmayı ve makrofaj infiltrasyonunu azaltmaktadır (66). 5-LO'nun inhibisyonu ateroskleroz üzerinde potansiyel bir terapötik hedef olabilir.

Peroksizom Proliferatörle Aktive Edilen Reseptörler

Peroksizom proliferatör tarafından aktive edilen reseptörler, yağ asitleri sensörleri olarak, obezite, ateroskleroz, diyabet, hiperlipidemi ve non-alkolik hepatosteatoz gibi çeşitli insan lipid metabolik hastalıklarında terapötik hedefler olmuşlardır. Tanımlanmış üç tip PPAR vardır: PPAR-alfa, PPARβ/δ ve PPARγ. Peroksizom proliferatörü ile aktive olan reseptörler anti-aterosklerotik etkilerinde bazı ortak özelliklere sahiptirler. ApoE-/- ve LDLR-/- farelerde PPARα ve PPARγ, köpük hücre oluşumunu ve ateroskleroz gelişimini engeller (67). Peroksizom proliferatörü ile aktive olan reseptörler, inflamasyon ve kolesterol homeostazı için kritik bir ara yüz teşkil edegelmişlerdir. Peroksizom proliferatörü ile aktive olan reseptörler ateroskleroz üzerinde potansiyel bir terapötik hedef teşkil edebilir.

KAYNAKLAR

1. Adams MR, Nakagomi A, Keech A, Robinson J, McCredie R, Bailey BP, et al. Carotid intima-media thickness is only weakly correlated with the extent and severity of coronary artery disease. 1995;92(8):2127-34.
2. Gao D, Ning N, Guo Y, Ning W, Niu X, Yang JJA. Computed tomography for detecting coronary artery plaques: a meta-analysis. 2011;219(2):603-9.
3. ONAT A, KELEŞ İ, ÇETİNKAYA A, BAŞAR Ö, YILDIRIM B, ERER B, et al. On yıllık TEKHARF çalışması verilerine göre Türk erişkinlerinde koroner kökenli ölüm ve olayların prevalansı yüksek. 2001;29(1):8-19.
4. Members WG, Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. 2010;121(7):e46-e215.
5. Davies MJ, Ho SY. Atlas of coronary artery disease: Lippincott Williams & Wilkins; 1998.
6. Smith J, Breslow JJJoim. The emergence of mouse models of atherosclerosis and their relevance to clinical research. 1997;242(2):99-109.
7. Ross RJNEjom. Atherosclerosis—an inflammatory disease. 1999;340(2):115-26.
8. Friedman M, Van den Bovenkamp GJTAjop. The pathogenesis of a coronary thrombus. 1966;48(1):19.
9. Libby P, Ridker PM, Hansson GKJN. Progress and challenges in translating the biology of atherosclerosis. 2011;473(7347):317-25.

10. Kanter JE, Kramer F, Barnhart S, Averill MM, Vivekanandan-Giri A, Vickery T, et al. Diabetes promotes an inflammatory macrophage phenotype and atherosclerosis through acyl-CoA synthetase 1. 2012;109(12):E715-E24.
11. Li J-J, Chen J-LJMh. Inflammation may be a bridge connecting hypertension and atherosclerosis. 2005;64(5):925-9.
12. Mallika V, Goswami B, Rajappa MJA. Atherosclerosis pathophysiology and the role of novel risk factors: a clinicobiochemical perspective. 2007;58(5):513-22.
13. Napoli C, Glass CK, Witztum JL, Deutsch R, D'Armiento FP, Palinski WJTL. Influence of maternal hypercholesterolaemia during pregnancy on progression of early atherosclerotic lesions in childhood: Fate of Early Lesions in Children (FELIC) study. 1999;354(9186):1234-41.
14. Williams KJ, Tabas IJCoil. The response-to-retention hypothesis of atherogenesis reinforced. 1998;9(5):471-4.
15. O'Brien KD, Allen MD, McDonald TO, Chait A, Harlan JM, Fishbein D, et al. Vascular cell adhesion molecule-1 is expressed in human coronary atherosclerotic plaques. Implications for the mode of progression of advanced coronary atherosclerosis. 1993;92(2):945-51.
16. Rosenfeld M, Ylä-Herttuala S, Lipton B, Ord V, Witztum J, Steinberg DJTAjop. Macrophage colony-stimulating factor mRNA and protein in atherosclerotic lesions of rabbits and humans. 1992;140(2):291.
17. Rosenfeld M, Ross RJAAOJotAHA, Inc. Macrophage and smooth muscle cell proliferation in atherosclerotic lesions of WHHL and comparably hypercholesterolemic fat-fed rabbits. 1990;10(5):680-7.
18. Gu L, Okada Y, Clinton SK, Gerard C, Sukhova GK, Libby P, et al. Absence of monocyte chemoattractant protein-1 reduces atherosclerosis in low density lipoprotein receptor–deficient mice. 1998;2(2):275-81.
19. Gosling J, Slaymaker S, Gu L, Tseng S, Zlot CH, Young SG, et al. MCP-1 deficiency reduces susceptibility to atherosclerosis in mice that overexpress human apolipoprotein B. 1999;103(6):773-8.
20. Libby PJC. Current concepts of the pathogenesis of the acute coronary syndromes. 2001;104(3):365-72.
21. Liu Y, Yu H, Zhang Y, Zhao YJMh. TLRs are important inflammatory factors in atherosclerosis and may be a therapeutic target. 2008;70(2):314-6.
22. Kaartinen M, Penttilä A, Kovanen PTJA, biology tajov. Mast cells of two types differing in neutral protease composition in the human aortic intima. Demonstration of tryptase-and tryptase/chymase-containing mast cells in normal intimas, fatty streaks, and the shoulder region of atheromas. 1994;14(6):966-72.
23. Hansson GK, Libby P, Tabas IJJoim. Inflammation and plaque vulnerability. 2015;278(5):483-93.
24. Chistiakov DA, Melnichenko AA, Grechko AV, Myasoedova VA, Orekhov ANJE, pathology m. Potential of anti-inflammatory agents for treatment of atherosclerosis. 2018;104(2):114-24.
25. Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull Jr W, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis: a report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. 1995;92(5):1355-74.

26. Price DT, Loscalzo JJTAjom. Cellular adhesion molecules and atherogenesis 1. 1999;107(1):85-97.
27. Afshar-Kharghan V, Thiagarajan PJCoih. Leukocyte adhesion and thrombosis. 2006;13(1):34-9.
28. Green D, Foiles N, Chan C, Kang J, Schreiner PJ, Liu KJS. An association between clotting factor VII and carotid intima-media thickness: the CARDIA study. 2010;41(7):1417-22.
29. Pasquali A, Trabetti E, Romanelli MG, Galavotti R, Martinelli N, Girelli D, et al. Detection of a large deletion in the P-selectin (SELP) gene. 2010;24(3):161-5.
30. Mantovani A, Garlanda C, Locati MJA, thrombosis,, biology v. Macrophage diversity and polarization in atherosclerosis: a question of balance. 2009;29(10):1419-23.
31. Virmani R, Kolodgie FD, Burke AP, Finn AV, Gold HK, Tulenko TN, et al. Atherosclerotic plaque progression and vulnerability to rupture: angiogenesis as a source of intraplaque hemorrhage. 2005;25(10):2054-61.
32. Fotis L, Agrogiannis G, Vlachos IS, Pantopoulou A, Margoni A, Kostaki M, et al. Intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 at the early stages of atherosclerosis in a rat model. 2012;26(2):243-50.
33. Ross TD, Coon BG, Yun S, Baeyens N, Tanaka K, Ouyang M, et al. Integrins in mechanotransduction. 2013;25(5):613-8.
34. Finney AC, Stokes KY, Pattillo CB, Orr AWJC, Sciences ML. Integrin signaling in atherosclerosis. 2017;74(12):2263-82.
35. Johnson JLJEroct. Matrix metalloproteinases: influence on smooth muscle cells and atherosclerotic plaque stability. 2007;5(2):265-82.
36. Luttun A, Lutgens E, Manderveld A, Maris K, Collen D, Carmeliet P, et al. Loss of matrix metalloproteinase-9 or matrix metalloproteinase-12 protects apolipoprotein E–deficient mice against atherosclerotic media destruction but differentially affects plaque growth. 2004;109(11):1408-14.
37. Rašić S, Rebić D, Hasić S, Rašić I, Delić Šarac MJMoi. Influence of malondialdehyde and matrix metalloproteinase-9 on progression of carotid atherosclerosis in chronic renal disease with cardiometabolic syndrome. 2015;2015.
38. Kuwahara S, Fukuoka M, Koan Y, Miyake H, Ono Y, Moriki A, et al. Subdural hyperintense band on diffusion-weighted imaging of chronic subdural hematoma indicates bleeding from the outer membrane. 2005;45(3):125-31.
39. Johnson JL, Baker AH, Oka K, Chan L, Newby AC, Jackson CL, et al. Suppression of atherosclerotic plaque progression and instability by tissue inhibitor of metalloproteinase-2: involvement of macrophage migration and apoptosis. 2006;113(20):2435-44.
40. Kuzuya M, Nakamura K, Sasaki T, Wu Cheng X, Itohara S, Iguchi AJA, thrombosis,, et al. Effect of MMP-2 deficiency on atherosclerotic lesion formation in apoE-deficient mice. 2006;26(5):1120-5.
41. Calabro P, Chang DW, Willerson JT, Yeh ETJJotACoC. Release of C-reactive protein in response to inflammatory cytokines by human adipocytes: linking obesity to vascular inflammation. 2005;46(6):1112-3.
42. Pepys MB, Hirschfield GMJTJoci. C-reactive protein: a critical update. 2003;111(12):1805-12.
43. Badimon L, Peña E, Arderiu G, Padró T, Slevin M, Vilahur G, et al. C-reactive protein in atherothrombosis and angiogenesis. 2018;9:430.
44. Li Y, Zhong X, Cheng G, Zhao C, Zhang L, Hong Y, et al. Hs-CRP and all-cause, cardiovascular, and cancer mortality risk: a meta-analysis. 2017;259:75-82.

45. Jones SAJTJoI. Directing transition from innate to acquired immunity: defining a role for IL-6. 2005;175(6):3463-8.

46. Aker S, Bantis C, Reis P, Kuhr N, Schwandt C, Grabensee B, et al. Influence of interleukin-6 G-174C gene polymorphism on coronary artery disease, cardiovascular complications and mortality in dialysis patients. 2009;24(9):2847-51.

47. Goldstein JL, Brown MSJN. Regulation of the mevalonate pathway. 1990;343(6257):425-30.

48. Alaarg A, Zheng KH, van der Valk FM, Da Silva AE, Versloot M, van Ufford LCQ, et al. Multiple pathway assessment to predict anti-atherogenic efficacy of drugs targeting macrophages in atherosclerotic plaques. 2016;82:51-9.

49. Alaarg A, Senders ML, Varela-Moreira A, Pérez-Medina C, Zhao Y, Tang J, et al. A systematic comparison of clinically viable nanomedicines targeting HMG-CoA reductase in inflammatory atherosclerosis. 2017;262:47-57.

50. Zapolska-Downar D, Siennicka A, Kaczmarczyk M, Kołodziej B, Naruszewicz MJLs. Simvastatin modulates TNFα-induced adhesion molecules expression in human endothelial cells. 2004;75(11):1287-302.

51. Schönbeck U, Libby PJC. Inflammation, immunity, and HMG-CoA reductase inhibitors: statins as antiinflammatory agents? 2004;109(21_suppl_1):II-18-II-26.

52. Wilensky RL, Shi Y, Mohler ER, Hamamdzic D, Burgert ME, Li J, et al. Inhibition of lipoprotein-associated phospholipase A 2 reduces complex coronary atherosclerotic plaque development. 2008;14(10):1059-66.

53. Lee Y-S, Jun H-SJMoi. Anti-inflammatory effects of GLP-1-based therapies beyond glucose control. 2016;2016.

54. Ban K, Noyan-Ashraf MH, Hoefer J, Bolz S-S, Drucker DJ, Husain MJC. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor–dependent and–independent pathways. 2008;117(18):2340-50.

55. Nagashima M, Watanabe T, Terasaki M, Tomoyasu M, Nohtomi K, Kim-Kaneyama J, et al. Native incretins prevent the development of atherosclerotic lesions in apolipoprotein E knockout mice. 2011;54(10):2649-59.

56. Tashiro Y, Sato K, Watanabe T, Nohtomi K, Terasaki M, Nagashima M, et al. A glucagon-like peptide-1 analog liraglutide suppresses macrophage foam cell formation and atherosclerosis. 2014;54:19-26.

57. Qamar A, Rader DJJCoil. Effect of interleukin 1β inhibition in cardiovascular disease. 2012;23(6):548-53.

58. Abbate A, Van Tassell BW, Biondi-Zoccai GGJB. Blocking interleukin-1 as a novel therapeutic strategy for secondary prevention of cardiovascular events. 2012;26(4):217-33.

59. Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ, Ridker PM, et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet 2018;391:319–328.

60. Naugler WE, Karin MJTimm. The wolf in sheep's clothing: the role of interleukin-6 in immunity, inflammation and cancer. 2008;14(3):109-19.

61. McInnes IB, Thompson L, Giles JT, Bathon JM, Salmon JE, Beaulieu AD, et al. Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study. 2015;74(4):694-702.

62. Nidorf SM, Eikelboom JW, Budgeon CA, et al. Low-dose colchicine for secondary prevention of cardiovascular disease. J Am Coll Cardiol 2013; 61:404-10.
63. Dogra S, Khullar GJIjod, venereology, leprology. Tumor necrosis factor-[alpha] antagonists: Side effects and their management. 2013;79:35.
64. Boshuizen MC, de Winther MPJA, thrombosis,, biology v. Interferons as essential modulators of atherosclerosis. 2015;35(7):1579-88.
65. Cipollone F, Mezzetti A, Fazia ML, Cuccurullo C, Iezzi A, Ucchino S, et al. Association between 5-lipoxygenase expression and plaque instability in humans. 2005;25(8):1665-70.
66. Vidal C, Gomez-Hernandez A, Sanchez-Galan E, Gonzalez A, Ortega L, Gomez-Gerique JA, et al. Licofelone, a balanced inhibitor of cyclooxygenase and 5-lipoxygenase, reduces inflammation in a rabbit model of atherosclerosis. 2007;320(1):108-16.
67. Li AC, Binder CJ, Gutierrez A, Brown KK, Plotkin CR, et al. Differential inhibition of macrophage foam-cell formation and atherosclerosis in mice by PPARα, β/δ, and γ. 2004;114(11):1564-76.