

REFERENCES:

1. Libby P, Hansson GK. From Focal Lipid Storage to Systemic Inflammation: JACC Review Topic of the Week. *J Am Coll Cardiol* 2019;**74**(12):1594-1607.
2. Guyton JR, Klemp KF. The lipid-rich core region of human atherosclerotic fibrous plaques. Prevalence of small lipid droplets and vesicles by electron microscopy. *Am J Pathol* 1989;**134**(3):705-17.
3. Parker F. An Electron Microscopic Study of Experimental Atherosclerosis. *Am J Pathol* 1960;**36**(1):19-53.
4. Baumer Y, McCurdy S, Jin X, Weatherby TM, Dey AK, Mehta NN, Yap JK, Kruth HS, Boisvert WA. Ultramorphological analysis of plaque advancement and cholesterol crystal formation in Ldlr knockout mouse atherosclerosis. *Atherosclerosis* 2019;**287**:100-111.
5. Nasiri M, Janoudi A, Vanderberg A, Frame M, Flegler C, Flegler S, Abela GS. Role of cholesterol crystals in atherosclerosis is unmasked by altering tissue preparation methods. *Microsc Res Tech* 2015;**78**(11):969-74.
6. Levene CI. The early lesions of atheroma in the coronary arteries. *J Pathol Bacteriol* 1956;**72**(1):79-82.
7. Aschoff A. *Zur Morphologie der lipoiden Substanzen*: Path. Anat. 47,1; 1909.

8. Katz SS, Shipley GG, Small DM. Physical chemistry of the lipids of human atherosclerotic lesions. Demonstration of a lesion intermediate between fatty streaks and advanced plaques. *J Clin Invest* 1976;**58**(1):200-11.
9. Bogren H, Larsson K. An X-Ray-Diffraction Study of Crystalline Cholesterol in Some Pathological Deposits in Man. *Biochim Biophys Acta* 1963;**75**:65-9.
10. Suhaimi JL, Chung CY, Lilledahl MB, Lim RS, Levi M, Tromberg BJ, Potma EO. Characterization of cholesterol crystals in atherosclerotic plaques using stimulated Raman scattering and second-harmonic generation microscopy. *Biophys J* 2012;**102**(8):1988-95.
11. Lehti S, Nguyen SD, Belevich I, Vihinen H, Heikkila HM, Soliymani R, Kakela R, Saksi J, Jauhiainen M, Grabowski GA, Kummu O, Horkko S, Baumann M, Lindsberg PJ, Jokitalo E, Kovanen PT, Oorni K. Extracellular Lipids Accumulate in Human Carotid Arteries as Distinct Three-Dimensional Structures and Have Proinflammatory Properties. *Am J Pathol* 2018;**188**(2):525-538.
12. Ho-Tin-Noe B, Vo S, Bayles R, Ferriere S, Ladjal H, Toumi S, Deschildre C, Ollivier V, Michel JB. Cholesterol crystallization in human atherosclerosis is triggered in smooth muscle cells during the transition from fatty streak to fibroatheroma. *J Pathol* 2017;**241**(5):671-682.
13. Baumer Y, McCurdy S, Weatherby TM, Mehta NN, Halbherr S, Halbherr P, Yamazaki N, Boisvert WA. Hyperlipidemia-induced cholesterol crystal production by endothelial cells promotes atherogenesis. *Nature Communications* 2017;**8**(1):1129.
14. Baumer Y, Ng Q, Sanda GE, Dey AK, Teague HL, Sorokin AV, Dagur PK, Silverman JJ, Harrington CL, Rodante JA, Rose SM, Varghese NJ, Belur AD, Goyal A, Gelfand JM, Springer DA, Bleck CK, Thomas CL, Yu ZX, Winge MC, Kruth HS, Marinkovich MP, Joshi AA, Playford MP, Mehta NN. Chronic skin inflammation accelerates macrophage cholesterol crystal formation and atherosclerosis. *JCI Insight* 2018;**3**(1).
15. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists' view. *Eur Heart J* 2013;**34**(10):719-28.
16. Shi X, Cai H, Wang F, Liu R, Xu X, Li M, Han Y, Yin Q, Ye R, Liu X. Cholesterol Crystals are Associated with Carotid Plaque Vulnerability: An Optical Coherence Tomography Study. *J Stroke Cerebrovasc Dis* 2020;**29**(2):104579.
17. Fujiyoshi K, Minami Y, Ishida K, Kato A, Katsura A, Muramatsu Y, Sato T, Kakizaki R, Nemoto T, Hashimoto T, Sato N, Meguro K, Shimohama T, Tojo T, Ako J. Incidence, factors, and clinical significance of cholesterol crystals in coronary plaque: An optical coherence tomography study. *Atherosclerosis* 2019;**283**:79-84.
18. Shi C, Kim T, Steiger S, Mulay SR, Klinkhammer BM, Bauerle T, Melica ME, Romagnani P, Mockel D, Baues M, Yang L, Brouns SLN, Heemskerk JWM, Braun A, Lammers T, Boor P, Anders HJ. Crystal Clots as Therapeutic Target in Cholesterol Crystal Embolism. *Circ Res* 2020;**126**(8):e37-e52.
19. Komatsu S, Takahashi S, Yutani C, Ohara T, Takewa M, Hirayama A, Kodama K. Spontaneous ruptured aortic plaque and injuries: insights for aging and acute aortic syndrome from non-obstructive general angioscopy. *J Cardiol* 2020;**75**(4):344-351.
20. Quinones A, Saric M. The cholesterol emboli syndrome in atherosclerosis. *Curr Atheroscler Rep* 2013;**15**(4):315.
21. Janoudi A, Shamoun FE, Kalavakunta JK, Abela GS. Cholesterol crystal induced arterial inflammation and destabilization of atherosclerotic plaque. *Eur Heart J* 2016;**37**(25):1959-67.
22. Corr EM, Cunningham CC, Dunne A. Cholesterol crystals activate Syk and PI3 kinase in human macrophages and dendritic cells. *Atherosclerosis* 2016;**251**:197-205.

23. Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, Abela GS, Franchi L, Nunez G, Schnurr M, Espevik T, Lien E, Fitzgerald KA, Rock KL, Moore KJ, Wright SD, Hornung V, Latz E. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. *Nature* 2011;**464**(7293):1357-61.
24. Freigang S, Ampenberger F, Spohn G, Heer S, Shamshiev AT, Kisielow J, Hersberger M, Yamamoto M, Bachmann MF, Kopf M. Nrf2 is essential for cholesterol crystal-induced inflammasome activation and exacerbation of atherosclerosis. *Eur J Immunol* 2011;**41**(7):2040-51.
25. Rajamaki K, Lappalainen J, Oorni K, Valimaki E, Matikainen S, Kovanen PT, Eklund KK. Cholesterol crystals activate the NLRP3 inflammasome in human macrophages: a novel link between cholesterol metabolism and inflammation. *PLoS One* 2010;**5**(7):e11765.
26. Geng YJ, Phillips JE, Mason RP, Casscells SW. Cholesterol crystallization and macrophage apoptosis: implication for atherosclerotic plaque instability and rupture. *Biochem Pharmacol* 2003;**66**(8):1485-92.
27. Nakayama M. Macrophage Recognition of Crystals and Nanoparticles. *Front Immunol* 2018;**9**:103.
28. Desai J, Foresto-Neto O, Honarpisheh M, Steiger S, Nakazawa D, Popper B, Buhl EM, Boor P, Mulay SR, Anders HJ. Particles of different sizes and shapes induce neutrophil necroptosis followed by the release of neutrophil extracellular trap-like chromatin. *Sci Rep* 2017;**7**(1):15003.
29. Mani AM, Chattopadhyay R, Singh NK, Rao GN. Cholesterol crystals increase vascular permeability by inactivating SHP2 and disrupting adherens junctions. *Free Radic Biol Med* 2018;**123**:72-84.
30. Pichavaram P, Mani AM, Singh NK, Rao GN. Cholesterol crystals promote endothelial cell and monocyte interactions via H2O2-mediated PP2A inhibition, NFkappaB activation and ICAM1 and VCAM1 expression. *Redox Biol* 2019;**24**:101180.
31. Samstad EO, Niyonzima N, Nymo S, Aune MH, Ryan L, Bakke SS, Lappegard KT, Brekke OL, Lambris JD, Damas JK, Latz E, Mollnes TE, Espevik T. Cholesterol crystals induce complement-dependent inflammasome activation and cytokine release. *J Immunol* 2014;**192**(6):2837-45.
32. Gravastrand CS, Steinkjer B, Halvorsen B, Landsem A, Skjelland M, Jacobsen EA, Woodruff TM, Lambris JD, Mollnes TE, Brekke OL, Espevik T, Rokstad AMA. Cholesterol Crystals Induce Coagulation Activation through Complement-Dependent Expression of Monocytic Tissue Factor. *J Immunol* 2019;**203**(4):853-863.
33. Varsano N, Fargion I, Wolf SG, Leiserowitz L, Addadi L. Formation of 3D cholesterol crystals from 2D nucleation sites in lipid bilayer membranes: implications for atherosclerosis. *J Am Chem Soc* 2015;**137**(4):1601-7.
34. Tangirala RK, Jerome WG, Jones NL, Small DM, Johnson WJ, Glick JM, Mahlberg FH, Rothblat GH. Formation of cholesterol monohydrate crystals in macrophage-derived foam cells. *J Lipid Res* 1994;**35**(1):93-104.
35. Abela GS. Cholesterol crystals piercing the arterial plaque and intima trigger local and systemic inflammation. *J Clin Lipidol* 2010;**4**(3):156-64.
36. Konikoff FM, Chung DS, Donovan JM, Small DM, Carey MC. Filamentous, helical, and tubular microstructures during cholesterol crystallization from bile. Evidence that cholesterol does not nucleate classic monohydrate plates. *J Clin Invest* 1992;**90**(3):1155-60.

37. Varsano N, Beghi F, Elad N, Pereiro E, Dadosh T, Pinkas I, Perez-Berna AJ, Jin X, Kruth HS, Leiserowitz L, Addadi L. Two polymorphic cholesterol monohydrate crystal structures form in macrophage culture models of atherosclerosis. *Proc Natl Acad Sci U S A* 2018;**115**(3):7662-7669.
38. Sheedy FJ, Grebe A, Rayner KJ, Kalantari P, Ramkhalawon B, Carpenter SB, Becker CE, Ediriweera HN, Mullick AE, Golenbock DT, Stuart LM, Latz E, Fitzgerald KA, Moore KJ. CD36 coordinates NLRP3 inflammasome activation by facilitating intracellular nucleation of soluble ligands into particulate ligands in sterile inflammation. *Nat Immunol* 2013;**14**(8):812-20.
39. Jin X, Dimitriadis EK, Liu Y, Combs CA, Chang J, Varsano N, Stempinski E, Flores R, Jackson SN, Muller L, Woods AS, Addadi L, Kruth HS. Macrophages Shed Excess Cholesterol in Unique Extracellular Structures Containing Cholesterol Microdomains. *Arterioscler Thromb Vasc Biol* 2018;**38**(7):1504-1518.
40. Vedre A, Pathak DR, Crimp M, Lum C, Koochesfahani M, Abela GS. Physical factors that trigger cholesterol crystallization leading to plaque rupture. *Atherosclerosis* 2009;**203**(1):89-96.
41. Kataoka Y, Puri R, Hammadah M, Duggal B, Uno K, Kapadia SR, Tuzcu EM, Nissen SE, Nicholls SJ. Cholesterol crystals associate with coronary plaque vulnerability in vivo. *J Am Coll Cardiol* 2015;**65**(6):630-2.
42. Kobayashi T, Higuchi Y, Komatsu S, Yutani C, Hirayama A, Kodama K. Visualization of Cholesterol Crystals Liberated From a Diseased Saphenous Vein Coronary Bypass Graft. *JACC Cardiovasc Interv* 2020.
43. Sugane H, Kataoka Y, Otsuka F, Yasuda S. Cholesterol-crystallized coronary atheroma as a potential precursor lesion causing acute coronary syndrome: a case report. *European Heart Journal - Case Reports* 2019;**3**(3).
44. Lazareth H, Karras A. Cholesterol Crystal Embolization after Transcatheter Aortic-Valve Replacement. *N Engl J Med* 2019;**381**(7):655.
45. Fang C, Dai J, Zhang S, Wang Y, Wang J, Li L, Wang Y, Yu H, Wei G, Zhang X, Feng N, Liu H, Xu M, Ren X, Ma L, Tu Y, Xing L, Hou J, Yu B. Culprit lesion morphology in young patients with ST-segment elevated myocardial infarction: A clinical, angiographic and optical coherence tomography study. *Atherosclerosis* 2019;**289**:94-100.
46. Villiger M, Otsuka K, Karanasos A, Doradla P, Ren J, Lippok N, Shishkov M, Daemen J, Diletti R, van Geuns RJ, Zijlstra F, van Soest G, Libby P, Regar E, Nadkarni SK, Bouma BE. Coronary Plaque Microstructure and Composition Modify Optical Polarization: A New Endogenous Contrast Mechanism for Optical Frequency Domain Imaging. *JACC Cardiovasc Imaging* 2018;**11**(11):1666-1676.
47. Abela GS, Kalavakunta JK, Janoudi A, Leffler D, Dhar G, Salehi N, Cohn J, Shah I, Karve M, Kotaru VPK, Gupta V, David S, Narisetty KK, Rich M, Vanderberg A, Pathak DR, Shamoun FE. Frequency of Cholesterol Crystals in Culprit Coronary Artery Aspirate During Acute Myocardial Infarction and Their Relation to Inflammation and Myocardial Injury. *Am J Cardiol* 2017;**120**(10):1699-1707.
48. Koide M, Matsuo A, Shimoo S, Takamatsu K, Kyodo A, Tsuji Y, Mera K, Tsubakimoto Y, Isodono K, Sakatani T, Inoue K, Fujita H. Cholesterol crystal depth in coronary atherosclerotic plaques: A novel index of plaque vulnerability using optical frequency domain imaging. *PLoS One* 2017;**12**(6):e0180303.

49. Nishimura S, Ehara S, Hasegawa T, Matsumoto K, Yoshikawa J, Shimada K. Cholesterol crystal as a new feature of coronary vulnerable plaques: An optical coherence tomography study. *J Cardiol* 2017;**69**(1):253-259.
50. Kataoka Y, Puri R, Hammadah M, Duggal B, Uno K, Kapadia SR, Tuzcu EM, Nissen SE, King P, Nicholls SJ. Sex Differences in Nonculprit Coronary Plaque Microstructures on Frequency-Domain Optical Coherence Tomography in Acute Coronary Syndromes and Stable Coronary Artery Disease. *Circ Cardiovasc Imaging* 2016;**9**(8).
51. Dai J, Tian J, Hou J, Xing L, Liu S, Ma L, Yu H, Ren X, Dong N, Yu B. Association between cholesterol crystals and culprit lesion vulnerability in patients with acute coronary syndrome: An optical coherence tomography study. *Atherosclerosis* 2016;**247**:111-7.
52. Warnatsch A, Ioannou M, Wang Q, Papayannopoulos V. Inflammation. Neutrophil extracellular traps license macrophages for cytokine production in atherosclerosis. *Science* 2015;**349**(6245):316-20.