

Podoplanin-positive cell-derived small extracellular vesicles contribute to cardiac amyloidosis after myocardial infarction

Pathologies	Type of cells
Myocardial infarction and heart failure ¹⁻⁶	Mesenchymal stromal cells
Cardiac Fibrosis ⁷⁻⁹	Mesenchymal stromal cells and early reactive fibroblasts
Thrombi and thrombo-inflammation ^{10,11}	Mesenchymal stromal cells
Deep vein thrombosis ^{12,13}	Mesenchymal stromal cells
Atherosclerotic lesion ^{6,14-17}	Mesenchymal stromal cells, Smooth muscle cells and macrophages
Aneurysm and High arteria shear ¹⁸⁻²⁰	Mesenchymal stromal cells
Calcification aortic valves ²¹	Mesenchymal stromal cells and fibroblast
Stroke ²²	Microglia
Alzheimer Disease ⁴	Mesenchymal and neural stromal cells
LPS-induced neuroinflammation ²³	Astrocytes and glial cells
Traumatic brain injury ^{24,25}	Astrocytes and glial cells
Gliosis and astrogliosis ²⁶	Astrocytes
Gliomas ^{27,28}	Astrocytes
Glioblastoma ⁴	Mesenchymal and neural stromal cells
Gout arthritis, psoriatic arthritis, unclassified arthritis (UA), parvovirus associated arthritis, reactive arthritis ^{29,30}	Mesenchymal stromal cells and fibroblast
Rheumatoid arthritis ²⁹⁻³⁴	Synovial fibroblasts
Psoriasis ^{34,35}	Synovial fibroblasts
Multiple sclerosis ³⁴	Mesenchymal stromal cells
Inflammatory bowel disease ³⁶	Mesenchymal stromal cells
Solid tumors ³⁷⁻³⁹	Cancer cells and CAF
Cancer associated thrombi ^{34,40}	Cancer cells and Cancer associated fibroblasts
Intestinal segmented filamentous bacterial infection ^{36,41}	Epithelial cells
Hypercaloric diet ^{42,43}	Mesenchymal stromal cells
Cirrhosis ⁴⁴	Fibroblast
Preeclampsia ⁴⁵	Villous stromal cells
Fallopian tubes inflammation ⁴⁶	Telocytes

Table S 1. Literature search about Podoplanin acquisition by mesenchymal stromal and other cell types in different pathologies. The table groups all the pathologies that have been characterized by de-novo Podoplanin acquisition in mesenchymal stromal or other cell types. Papers that describe each pathology are listed in the references for Table 1. The type of cells that de-novo acquire Podoplanin are mostly mesenchymal stromal cells, unless the equivalent type of cells in the central nervous system or cancer tissue.

Pathologies	Type of cells
Myocardial infarction and heart failure ⁴⁷⁻⁶¹	Mesenchymal stromal cells and immune cells
Thrombosis ⁶²⁻⁶⁵	Mesenchymal stromal cells and immune cells
Atherosclerosis ⁶⁶⁻⁷²	Adipose cells and macrophages
Atherosclerosis ^{57,63-65,67-75}	Mesenchymal stromal cells and immune cells
Aneurysm and aortic aneurysm ^{57,63,76-78}	Mesenchymal stromal cells and immune cells
Endocarditis ⁷⁹	Mesenchymal stromal cells and immune cells
Stroke and cerebral ischemia ^{59,63,80}	Neuroinflammation
Alzheimer Disease ⁸¹	Astrocytes
Neuroinflammation ^{59,63,81-83}	Macrophages
Cerebral Toxoplasma Gondii infection ^{84,85}	Inflammatory cells
Peripheral nerve damage ^{80,86-88}	Nerve
Corneal inflammation ⁸⁹	Nerve
Depression ⁹⁰⁻⁹²	Microglia
Sleep deprivation ⁹³	Immune cells
Rheumatoid arthritis ^{32,59,63,94-102}	Synovium- Mesenchymal stromal cells and inflammatory cells
Psoriasis ^{59,99,103}	Macrophages
Multiple sclerosis ⁸¹	Neurons
Solid tumors ^{59,63,104-107}	Cancer cells, CAF, immune cells
Intestinal segmented filamentous bacterial infection ^{41,59,84,108,109}	Epithelial cells and macrophages
Obesity and Insulin resistance ¹¹⁰⁻¹¹⁴	Adipocytes, epithelial cells, and macrophages
Liver Injury and autoimmune hepatitis ^{115,116}	Stromal cells and stellate cells
Hepatic fibrogenesis ¹¹⁶	Stromal cells and stellate cells
Lung bacterial infection ^{84,117,118}	Lung epithelia
Lung infection associated with atherosclerosis ¹¹⁹	Immune cells
Diabetic nephropathy ^{120,121}	Podocytes, immune and stromal cells
Tubulointerstitial fibrosis in kidney ¹²²	Podocytes and inflammatory cells
Osteoporosis ¹²³	Immune cells
Endometriosis ¹²⁴	Mesenchymal stromal cells and immune cells

Table S 2. Literature search about Serum Amyloid A3 (SAA3) deposition as amyloidosis and acquisition by mesenchymal stromal and other cell types in different pathologies. The table groups all the pathologies that have been characterized by SAA3 deposition as amyloidosis and acquisition by mesenchymal stromal or other cell types. Papers that describe each pathology are listed in the references for Table 2. The type of pathologies in which SAA3 amyloidosis is present and SAA3 is the dominant cytokine are the same pathologies characterized by Podoplanin acquisition. Table 1 and Table 2 correlate Podoplanin acquisition and SAA3 amyloidosis in different pathologies.

References for Table 1 and 2

1. Cimini, M., Cannata, A., Pasquinelli, G., Rota, M., and Goichberg, P. (2017). Phenotypically heterogeneous podoplanin-expressing cell populations are associated with the lymphatic vessel growth and fibrogenic responses in the acutely and chronically infarcted myocardium. *PLoS One* 12, e0173927. 10.1371/journal.pone.0173927.
2. Cimini, M., Garikipati, V.N.S., de Lucia, C., Cheng, Z., Wang, C., Truongcao, M.M., Lucchese, A.M., Roy, R., Benedict, C., Goukassian, D.A., et al. (2019). Podoplanin neutralization improves cardiac remodeling and function after acute myocardial infarction. *JCI Insight* 5. 10.1172/jci.insight.126967.
3. Cimini, M., and Kishore, R. (2021). Role of Podoplanin-Positive Cells in Cardiac Fibrosis and Angiogenesis After Ischemia. *Front Physiol* 12, 667278. 10.3389/fphys.2021.667278.
4. Danielyan, L., Schwab, M., Siegel, G., Brawek, B., Garaschuk, O., Asavapanumas, N., Buadze, M., Lourhmati, A., Wendel, H.P., Avci-Adali, M., et al. (2020). Cell motility and migration as determinants of stem cell efficacy. *EBioMedicine* 60, 102989. 10.1016/j.ebiom.2020.102989.
5. Stellato, M., Czepiel, M., Distler, O., Blyszczuk, P., and Kania, G. (2019). Identification and Isolation of Cardiac Fibroblasts From the Adult Mouse Heart Using Two-Color Flow Cytometry. *Front Cardiovasc Med* 6, 105. 10.3389/fcvm.2019.00105.
6. Kholova, I., Dragneva, G., Cermakova, P., Laidinen, S., Kaskenpaa, N., Hazes, T., Cermakova, E., Steiner, I., and Yla-Herttuala, S. (2011). Lymphatic vasculature is increased in heart valves, ischaemic and inflamed hearts and in cholesterol-rich and calcified atherosclerotic lesions. *Eur J Clin Invest* 41, 487-497. 10.1111/j.1365-2362.2010.02431.x.
7. Lim, S.E., Joseph, M.D., de Winde, C.M., Acton, S.E., and Simoncelli, S. (2023). Quantitative single molecule analysis of podoplanin clustering in fibroblastic reticular cells uncovers CD44 function. *Open Biol* 13, 220377. 10.1098/rsob.220377.
8. Lu, S., and Qiao, X. (2021). Single-cell profiles of human bone marrow-derived mesenchymal stromal cells after IFN-gamma and TNF-alpha licensing. *Gene* 771, 145347. 10.1016/j.gene.2020.145347.
9. Manta, L., Rusu, M.C., and Pop, F. (2018). What podoplanin tells us about cells with telopodes. *Ann Anat* 218, 124-128. 10.1016/j.aanat.2018.04.001.
10. Meng, D., Luo, M., and Liu, B. (2021). The Role of CLEC-2 and Its Ligands in Thromboinflammation. *Front Immunol* 12, 688643. 10.3389/fimmu.2021.688643.
11. Rakocovic, J., Kojic, S., Orlic, D., Stankovic, G., Ostojic, M., Petrovic, O., Zaletel, I., Puskas, N., Todorovic, V., and Labudovic-Borovic, M. (2016). Co-expression of vascular and lymphatic endothelial cell markers on early endothelial cells present in aspirated coronary thrombi from patients with ST-elevation myocardial infarction. *Exp Mol Pathol* 100, 31-38. 10.1016/j.yexmp.2015.11.028.
12. Payne, H., Ponomaryov, T., Watson, S.P., and Brill, A. (2017). Mice with a deficiency in CLEC-2 are protected against deep vein thrombosis. *Blood* 129, 2013-2020. 10.1182/blood-2016-09-742999.
13. Pollitt, A.Y., Poulter, N.S., Gitz, E., Navarro-Nunez, L., Wang, Y.J., Hughes, C.E., Thomas, S.G., Nieswandt, B., Douglas, M.R., Owen, D.M., et al. (2014). Syk and Src family kinases regulate C-type lectin receptor 2 (CLEC-2)-mediated clustering of podoplanin and platelet adhesion to lymphatic endothelial cells. *J Biol Chem* 289, 35695-35710. 10.1074/jbc.M114.584284.
14. Ciavarella, C., Gallitto, E., Ricci, F., Buzzi, M., Stella, A., and Pasquinelli, G. (2017). The crosstalk between vascular MSCs and inflammatory mediators determines the pro-calcific remodelling of human atherosclerotic aneurysm. *Stem Cell Res Ther* 8, 99. 10.1186/s13287-017-0554-x.
15. Hatakeyama, K., Kaneko, M.K., Kato, Y., Ishikawa, T., Nishihira, K., Tsujimoto, Y., Shibata, Y., Ozaki, Y., and Asada, Y. (2012). Podoplanin expression in advanced atherosclerotic lesions of human aortas. *Thromb Res* 129, e70-76. 10.1016/j.thromres.2012.01.003.
16. Shi, C., Men, L., Yu, C., Yao, J., Bai, R., Yang, Y., Sun, L., Sun, G., Song, G., Zhang, Y., et al. (2017). Atherosclerosis associated with dynamic inflammation changes after multifactorial intervention in short-duration type 2 diabetes: A randomized, controlled, 10-year follow-up trial. *J Diabetes Complications* 31, 1286-1292. 10.1016/j.jdiacomp.2017.05.008.

17. Zazzeroni, L., Faggioli, G., and Pasquinelli, G. (2018). Mechanisms of Arterial Calcification: The Role of Matrix Vesicles. *Eur J Vasc Endovasc Surg* 55, 425-432. 10.1016/j.ejvs.2017.12.009.
18. Lombard, S.E., Pollitt, A.Y., Hughes, C.E., Di, Y., McKinnon, T., O'Callaghan C, A., and Watson, S.P. (2018). Mouse podoplanin supports adhesion and aggregation of platelets under arterial shear: A novel mechanism of haemostasis. *Platelets* 29, 716-722. 10.1080/09537104.2017.1356919.
19. Ward, L.S.C., Sheriff, L., Marshall, J.L., Manning, J.E., Brill, A., Nash, G.B., and McGettrick, H.M. (2019). Podoplanin regulates the migration of mesenchymal stromal cells and their interaction with platelets. *J Cell Sci* 132. 10.1242/jcs.222067.
20. Xu, C., Gao, X., Wei, Q., Nakahara, F., Zimmerman, S.E., Mar, J., and Frenette, P.S. (2018). Stem cell factor is selectively secreted by arterial endothelial cells in bone marrow. *Nat Commun* 9, 2449. 10.1038/s41467-018-04726-3.
21. Napankangas, J., Ohtonen, P., Ohukainen, P., Weisell, J., Vaisanen, T., Peltonen, T., Taskinen, P., and Rysa, J. (2019). Increased mesenchymal podoplanin expression is associated with calcification in aortic valves. *Cardiovasc Pathol* 39, 30-37. 10.1016/j.carpath.2018.11.006.
22. Meng, D., Ma, X., Li, H., Wu, X., Cao, Y., Miao, Z., and Zhang, X. (2020). A Role of the Podoplanin-CLEC-2 Axis in Promoting Inflammatory Response After Ischemic Stroke in Mice. *Neurotox Res*. 10.1007/s12640-020-00295-w.
23. Song, Y., Shen, J., Lin, Y., Shen, J., Wu, X., Yan, Y., Zhou, L., Zhang, H., Zhou, Y., Cao, M., and Liu, Y. (2014). Up-regulation of podoplanin involves in neuronal apoptosis in LPS-induced neuroinflammation. *Cell Mol Neurobiol* 34, 839-849. 10.1007/s10571-014-0060-y.
24. Dias, D.O., Kim, H., Holl, D., Werne Solnestam, B., Lundeborg, J., Carlen, M., Goritz, C., and Frisen, J. (2018). Reducing Pericyte-Derived Scarring Promotes Recovery after Spinal Cord Injury. *Cell* 173, 153-165 e122. 10.1016/j.cell.2018.02.004.
25. Fei, M., Wang, H., Zhou, M., Deng, C., Zhang, L., and Han, Y. (2020). Podoplanin influences the inflammatory phenotypes and mobility of microglia in traumatic brain injury. *Biochem Biophys Res Commun* 523, 361-367. 10.1016/j.bbrc.2019.12.003.
26. Lowe, K.L., Finney, B.A., Deppermann, C., Hagerling, R., Gazit, S.L., Frampton, J., Buckley, C., Camerer, E., Nieswandt, B., Kiefer, F., and Watson, S.P. (2015). Podoplanin and CLEC-2 drive cerebrovascular patterning and integrity during development. *Blood* 125, 3769-3777. 10.1182/blood-2014-09-603803.
27. Chandramohan, V., Bao, X., Kato Kaneko, M., Kato, Y., Keir, S.T., Szafranski, S.E., Kuan, C.T., Pastan, I.H., and Bigner, D.D. (2013). Recombinant anti-podoplanin (NZ-1) immunotoxin for the treatment of malignant brain tumors. *Int J Cancer* 132, 2339-2348. 10.1002/ijc.27919.
28. Kolar, K., Freitas-Andrade, M., Bechberger, J.F., Krishnan, H., Goldberg, G.S., Naus, C.C., and Sin, W.C. (2015). Podoplanin: a marker for reactive gliosis in gliomas and brain injury. *J Neuropathol Exp Neurol* 74, 64-74. 10.1097/NEN.0000000000000150.
29. Del Rey, M.J., Fare, R., Izquierdo, E., Usategui, A., Rodriguez-Fernandez, J.L., Suarez-Fueyo, A., Canete, J.D., and Pablos, J.L. (2014). Clinicopathological correlations of podoplanin (gp38) expression in rheumatoid synovium and its potential contribution to fibroblast platelet crosstalk. *PLoS One* 9, e99607. 10.1371/journal.pone.0099607.
30. Choi, I.Y., Karpus, O.N., Turner, J.D., Hardie, D., Marshall, J.L., de Hair, M.J.H., Maijer, K.I., Tak, P.P., Raza, K., Hamann, J., et al. (2017). Stromal cell markers are differentially expressed in the synovial tissue of patients with early arthritis. *PLoS One* 12, e0182751. 10.1371/journal.pone.0182751.
31. Mizoguchi, F., Slowikowski, K., Wei, K., Marshall, J.L., Rao, D.A., Chang, S.K., Nguyen, H.N., Noss, E.H., Turner, J.D., Earp, B.E., et al. (2018). Functionally distinct disease-associated fibroblast subsets in rheumatoid arthritis. *Nat Commun* 9, 789. 10.1038/s41467-018-02892-y.
32. Nakamura, T., Higashi, S., Tomoda, K., Tsukano, M., and Baba, S. (2007). Efficacy of etanercept in patients with AA amyloidosis secondary to rheumatoid arthritis. *Clin Exp Rheumatol* 25, 518-522.
33. Noack, M., Ndongo-Thiam, N., and Miossec, P. (2016). Interaction among activated lymphocytes and mesenchymal cells through podoplanin is critical for a high IL-17 secretion. *Arthritis Res Ther* 18, 148. 10.1186/s13075-016-1046-6.
34. Quintanilla, M., Montero-Montero, L., Renart, J., and Martin-Villar, E. (2019). Podoplanin in Inflammation and Cancer. *Int J Mol Sci* 20. 10.3390/ijms20030707.

35. Noack, M., Ndongo-Thiam, N., and Miossec, P. (2016). Role of podoplanin in the high interleukin-17A secretion resulting from interactions between activated lymphocytes and psoriatic skin-derived mesenchymal cells. *Clin Exp Immunol* 186, 64-74. 10.1111/cei.12830.
36. Basic, M., Peppermuller, P.P., Bolsega, S., Bleich, A., Bornemann, M., Bode, U., and Buettner, M. (2020). Lymph Node Stromal Cells From Different Draining Areas Distinctly Regulate the Development of Chronic Intestinal Inflammation. *Front Immunol* 11, 549473. 10.3389/fimmu.2020.549473.
37. Krishnan, H., Rayes, J., Miyashita, T., Ishii, G., Retzbach, E.P., Sheehan, S.A., Takemoto, A., Chang, Y.W., Yoneda, K., Asai, J., et al. (2018). Podoplanin: An emerging cancer biomarker and therapeutic target. *Cancer Sci* 109, 1292-1299. 10.1111/cas.13580.
38. Martin-Villar, E., Borda-d'Agua, B., Carrasco-Ramirez, P., Renart, J., Parsons, M., Quintanilla, M., and Jones, G.E. (2015). Podoplanin mediates ECM degradation by squamous carcinoma cells through control of invadopodia stability. *Oncogene* 34, 4531-4544. 10.1038/onc.2014.388.
39. Suzuki, H., Kaneko, M.K., and Kato, Y. (2022). Roles of Podoplanin in Malignant Progression of Tumor. *Cells* 11. 10.3390/cells11030575.
40. Pula, B., Witkiewicz, W., Dziegiel, P., and Podhorska-Okolow, M. (2013). Significance of podoplanin expression in cancer-associated fibroblasts: a comprehensive review. *Int J Oncol* 42, 1849-1857. 10.3892/ijo.2013.1887.
41. Wang, Y., Yin, Y., Chen, X., Zhao, Y., Wu, Y., Li, Y., Wang, X., Chen, H., and Xiang, C. (2019). Induction of Intestinal Th17 Cells by Flagellins From Segmented Filamentous Bacteria. *Front Immunol* 10, 2750. 10.3389/fimmu.2019.02750.
42. Hepler, C., Shan, B., Zhang, Q., Henry, G.H., Shao, M., Vishvanath, L., Ghaben, A.L., Mobley, A.B., Strand, D., Hon, G.C., and Gupta, R.K. (2018). Identification of functionally distinct fibro-inflammatory and adipogenic stromal subpopulations in visceral adipose tissue of adult mice. *Elife* 7. 10.7554/eLife.39636.
43. Taran, D., Tarlui, V.N., Ceausu, R.A., Cimpean, A.M., Raica, M., and Sarb, S. (2019). Podoplanin and PROX1 Expression in Hypercaloric Diet-induced Pancreatic Injuries. *In Vivo* 33, 1157-1163. 10.21873/invivo.11586.
44. Eckert, C., Kim, Y.O., Julich, H., Heier, E.C., Klein, N., Krause, E., Tschernig, T., Kornek, M., Lammert, F., Schuppan, D., and Lukacs-Kornek, V. (2016). Podoplanin discriminates distinct stromal cell populations and a novel progenitor subset in the liver. *Am J Physiol Gastrointest Liver Physiol* 310, G1-12. 10.1152/ajpgi.00344.2015.
45. Onak Kandemir, N., Barut, F., Barut, A., Birol, I.E., Dogan Gun, B., and Ozdamar, S.O. (2019). Biological importance of podoplanin expression in chorionic villous stromal cells and its relationship to placental pathologies. *Sci Rep* 9, 14230. 10.1038/s41598-019-50652-9.
46. Urban, L., Miko, M., Kajanova, M., Bozikova, S., Mrazova, H., and Varga, I. (2016). Telocytes (interstitial Cajal-like cells) in human Fallopian tubes. *Bratisl Lek Listy* 117, 263-267. 10.4149/bl_2016_051.
47. Bausserman, L.L., Sadaniantz, A., Saritelli, A.L., Martin, V.L., Nugent, A.M., Sady, S.P., and Herbert, P.N. (1989). Time course of serum amyloid A response in myocardial infarction. *Clin Chim Acta* 184, 297-305. 10.1016/0009-8981(89)90063-6.
48. Casl, M.T., Surina, B., Glojnaric-Spasic, I., Pape, E., Jagarinec, N., and Kranjcevic, S. (1995). Serum amyloid A protein in patients with acute myocardial infarction. *Ann Clin Biochem* 32 (Pt 2), 196-200. 10.1177/000456329503200212.
49. Clifton, P.M., Mackinnon, A.M., and Barter, P.J. (1985). Effects of serum amyloid A protein (SAA) on composition, size, and density of high density lipoproteins in subjects with myocardial infarction. *J Lipid Res* 26, 1389-1398.
50. Ji, H., Chen, S., Hu, Q., He, Y., Zhou, L., Xie, J., Pan, H., Tong, X., and Wu, C. (2023). Investigating the Correlation between Serum Amyloid A and Infarct-Related Artery Patency Prior to Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction Patients. *Angiology*, 33197231183031. 10.1177/00033197231183031.
51. Buhl, E.M., Djudjaj, S., Klinkhammer, B.M., Ermert, K., Puellas, V.G., Lindenmeyer, M.T., Cohen, C.D., He, C., Borkham-Kamphorst, E., Weiskirchen, R., et al. (2020). Dysregulated mesenchymal PDGFR-beta drives kidney fibrosis. *EMBO Mol Med* 12, e11021. 10.15252/emmm.201911021.
52. Johnson, B.D., Kip, K.E., Marroquin, O.C., Ridker, P.M., Kelsey, S.F., Shaw, L.J., Pepine, C.J., Sharaf, B., Bairey Merz, C.N., Sopko, G., et al. (2004). Serum amyloid A as a predictor of coronary artery disease and cardiovascular outcome in women: the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation* 109, 726-732. 10.1161/01.CIR.0000115516.54550.B1.

53. Katayama, T., Nakashima, H., Honda, Y., Suzuki, S., Yamamoto, T., Iwasaki, Y., and Yano, K. (2007). The relationship between acute phase serum amyloid A (SAA) protein concentrations and left ventricular systolic function in acute myocardial infarction patients treated with primary coronary angioplasty. *Int Heart J* 48, 45-55. 10.1536/ihj.48.45.
54. Katayama, T., Nakashima, H., Takagi, C., Honda, Y., Suzuki, S., Iwasaki, Y., Yamamoto, T., Yoshioka, M., and Yano, K. (2006). Serum amyloid a protein as a predictor of cardiac rupture in acute myocardial infarction patients following primary coronary angioplasty. *Circ J* 70, 530-535. 10.1253/circj.70.530.
55. Katayama, T., Nakashima, H., Takagi, C., Honda, Y., Suzuki, S., Iwasaki, Y., and Yano, K. (2005). Prognostic value of serum amyloid A protein in patients with acute myocardial infarction. *Circ J* 69, 1186-1191. 10.1253/circj.69.1186.
56. Kosuge, M., Ebina, T., Ishikawa, T., Hibi, K., Tsukahara, K., Okuda, J., Iwahashi, N., Ozaki, H., Yano, H., Kusama, I., et al. (2007). Serum amyloid A is a better predictor of clinical outcomes than C-reactive protein in non-ST-segment elevation acute coronary syndromes. *Circ J* 71, 186-190. 10.1253/circj.71.186.
57. Morrow, D.A., Rifai, N., Antman, E.M., Weiner, D.L., McCabe, C.H., Cannon, C.P., and Braunwald, E. (2000). Serum amyloid A predicts early mortality in acute coronary syndromes: A TIMI 11A substudy. *J Am Coll Cardiol* 35, 358-362. 10.1016/s0735-1097(99)00574-4.
58. Oerlemans, M., Rutten, K.H.G., Minnema, M.C., Raymakers, R.A.P., Asselbergs, F.W., and de Jonge, N. (2019). Cardiac amyloidosis: the need for early diagnosis. *Neth Heart J* 27, 525-536. 10.1007/s12471-019-1299-1.
59. Tannock, L.R., De Beer, M.C., Ji, A., Shridas, P., Noffsinger, V.P., den Hartigh, L., Chait, A., De Beer, F.C., and Webb, N.R. (2018). Serum amyloid A3 is a high density lipoprotein-associated acute-phase protein. *J Lipid Res* 59, 339-347. 10.1194/jlr.M080887.
60. Wilson, P.G., Thompson, J.C., Shridas, P., McNamara, P.J., de Beer, M.C., de Beer, F.C., Webb, N.R., and Tannock, L.R. (2018). Serum Amyloid A Is an Exchangeable Apolipoprotein. *Arterioscler Thromb Vasc Biol* 38, 1890-1900. 10.1161/ATVBAHA.118.310979.
61. Zewinger, S., Drechsler, C., Kleber, M.E., Dressel, A., Riffel, J., Triem, S., Lehmann, M., Kopecky, C., Saemann, M.D., Lepper, P.M., et al. (2015). Serum amyloid A: high-density lipoproteins interaction and cardiovascular risk. *Eur Heart J* 36, 3007-3016. 10.1093/eurheartj/ehv352.
62. Chami, B., Barrie, N., Cai, X., Wang, X., Paul, M., Morton-Chandra, R., Sharland, A., Dennis, J.M., Freedman, S.B., and Witting, P.K. (2015). Serum amyloid A receptor blockade and incorporation into high-density lipoprotein modulates its pro-inflammatory and pro-thrombotic activities on vascular endothelial cells. *Int J Mol Sci* 16, 11101-11124. 10.3390/ijms160511101.
63. Papa, R., and Lachmann, H.J. (2018). Secondary, AA, Amyloidosis. *Rheum Dis Clin North Am* 44, 585-603. 10.1016/j.rdc.2018.06.004.
64. Song, C., Hsu, K., Yamen, E., Yan, W., Fock, J., Witting, P.K., Geczy, C.L., and Freedman, S.B. (2009). Serum amyloid A induction of cytokines in monocytes/macrophages and lymphocytes. *Atherosclerosis* 207, 374-383. 10.1016/j.atherosclerosis.2009.05.007.
65. Song, C., Shen, Y., Yamen, E., Hsu, K., Yan, W., Witting, P.K., Geczy, C.L., and Freedman, S.B. (2009). Serum amyloid A may potentiate prothrombotic and proinflammatory events in acute coronary syndromes. *Atherosclerosis* 202, 596-604. 10.1016/j.atherosclerosis.2008.04.049.
66. Chait, A., Wang, S., Goodspeed, L., Gomes, D., Turk, K.E., Wietecha, T., Tang, J., Storey, C., O'Brien, K.D., Rubinow, K.B., et al. (2021). Sexually Dimorphic Relationships Among Saa3 (Serum Amyloid A3), Inflammation, and Cholesterol Metabolism Modulate Atherosclerosis in Mice. *Arterioscler Thromb Vasc Biol* 41, e299-e313. 10.1161/ATVBAHA.121.316066.
67. De Beer, M.C., Wroblewski, J.M., Noffsinger, V.P., Rateri, D.L., Howatt, D.A., Balakrishnan, A., Ji, A., Shridas, P., Thompson, J.C., van der Westhuyzen, D.R., et al. (2014). Deficiency of endogenous acute phase serum amyloid A does not affect atherosclerotic lesions in apolipoprotein E-deficient mice. *Arterioscler Thromb Vasc Biol* 34, 255-261. 10.1161/ATVBAHA.113.302247.
68. Reardon, C.A. (2021). Saa3 Deficiency Identifies a Sexually Dimorphic Effect on Atherosclerosis That May Be Mediated In Part by Alterations in Trem2 Expression in Macrophages. *Arterioscler Thromb Vasc Biol* 41, 1890-1892. 10.1161/ATVBAHA.121.316292.

69. Shridas, P., and Tannock, L.R. (2019). Role of serum amyloid A in atherosclerosis. *Curr Opin Lipidol* 30, 320-325. 10.1097/MOL.0000000000000616.
70. Thompson, J.C., Jayne, C., Thompson, J., Wilson, P.G., Yoder, M.H., Webb, N., and Tannock, L.R. (2015). A brief elevation of serum amyloid A is sufficient to increase atherosclerosis. *J Lipid Res* 56, 286-293. 10.1194/jlr.M054015.
71. Thompson, J.C., Wilson, P.G., Shridas, P., Ji, A., de Beer, M., de Beer, F.C., Webb, N.R., and Tannock, L.R. (2018). Serum amyloid A3 is pro-atherogenic. *Atherosclerosis* 268, 32-35. 10.1016/j.atherosclerosis.2017.11.011.
72. Wilson, P.G., Thompson, J.C., Webb, N.R., de Beer, F.C., King, V.L., and Tannock, L.R. (2008). Serum amyloid A, but not C-reactive protein, stimulates vascular proteoglycan synthesis in a pro-atherogenic manner. *Am J Pathol* 173, 1902-1910. 10.2353/ajpath.2008.080201.
73. Hua, S., Song, C., Geczy, C.L., Freedman, S.B., and Witting, P.K. (2009). A role for acute-phase serum amyloid A and high-density lipoprotein in oxidative stress, endothelial dysfunction and atherosclerosis. *Redox Rep* 14, 187-196. 10.1179/135100009X12525712409490.
74. Ji, A., Trumbauer, A.C., Noffsinger, V.P., de Beer, F.C., Webb, N.R., Tannock, L.R., and Shridas, P. (2023). Serum amyloid A augments the atherogenic effects of cholesteryl ester transfer protein. *J Lipid Res* 64, 100365. 10.1016/j.jlr.2023.100365.
75. King, V.L., Thompson, J., and Tannock, L.R. (2011). Serum amyloid A in atherosclerosis. *Curr Opin Lipidol* 22, 302-307. 10.1097/MOL.0b013e3283488c39.
76. Shridas, P., Ji, A., Trumbauer, A.C., Noffsinger, V.P., Leung, S.W., Dugan, A.J., Thatcher, S.E., Cassis, L.A., de Beer, F.C., Webb, N.R., and Tannock, L.R. (2022). Adipocyte-Derived Serum Amyloid A Promotes Angiotensin II-Induced Abdominal Aortic Aneurysms in Obese C57BL/6J Mice. *Arterioscler Thromb Vasc Biol* 42, 632-643. 10.1161/ATVBAHA.121.317225.
77. Shridas, P., Ji, A., Trumbauer, A.C., Noffsinger, V.P., Meredith, L.W., de Beer, F.C., Mullick, A.E., Webb, N.R., Karounos, D.G., and Tannock, L.R. (2023). Antisense Oligonucleotide Targeting Hepatic Serum Amyloid A Limits the Progression of Angiotensin II-Induced Abdominal Aortic Aneurysm Formation. *bioRxiv*. 10.1101/2023.08.22.554377.
78. Shridas, P., Patrick, A.C., and Tannock, L.R. (2021). Role of Serum Amyloid A in Abdominal Aortic Aneurysm and Related Cardiovascular Diseases. *Biomolecules* 11. 10.3390/biom11121883.
79. Nakano, S., Ikebe, E., Tsukamoto, Y., Wang, Y., Matsumoto, T., Mitsui, T., Yahiro, T., Inoue, K., Kawazato, H., Yasuda, A., et al. (2013). Commensal microbiota contributes to chronic endocarditis in TAX1BP1 deficient mice. *PLoS One* 8, e73205. 10.1371/journal.pone.0073205.
80. Carabias, C.S., Castano-Leon, A.M., Blanca Navarro, B., Panero, I., Eiriz, C., Gomez, P.A., Egea, J., and Lagares, A. (2020). Serum Amyloid A1 as a Potential Intracranial and Extracranial Clinical Severity Biomarker in Traumatic Brain Injury. *J Intensive Care Med* 35, 1180-1195. 10.1177/0885066619837913.
81. Barbierato, M., Borri, M., Facci, L., Zusso, M., Skaper, S.D., and Giusti, P. (2017). Expression and Differential Responsiveness of Central Nervous System Glial Cell Populations to the Acute Phase Protein Serum Amyloid A. *Sci Rep* 7, 12158. 10.1038/s41598-017-12529-7.
82. Giladi, A., Wagner, L.K., Li, H., Dorr, D., Medaglia, C., Paul, F., Shemer, A., Jung, S., Yona, S., Mack, M., et al. (2020). Cxcl10(+) monocytes define a pathogenic subset in the central nervous system during autoimmune neuroinflammation. *Nat Immunol* 21, 525-534. 10.1038/s41590-020-0661-1.
83. Lin, A., Liu, J., Gong, P., Chen, Y., Zhang, H., Zhang, Y., and Yu, Y. (2020). Serum amyloid A inhibits astrocyte migration via activating p38 MAPK. *J Neuroinflammation* 17, 254. 10.1186/s12974-020-01924-z.
84. De Buck, M., Gouwy, M., Wang, J.M., Van Snick, J., Opdenakker, G., Struyf, S., and Van Damme, J. (2016). Structure and Expression of Different Serum Amyloid A (SAA) Variants and their Concentration-Dependent Functions During Host Insults. *Curr Med Chem* 23, 1725-1755. 10.2174/0929867323666160418114600.
85. Kobayashi, K., Umeda, K., Ihara, F., Tanaka, S., Yamagishi, J., Suzuki, Y., and Nishikawa, Y. (2019). Transcriptome analysis of the effect of C-C chemokine receptor 5 deficiency on cell response to *Toxoplasma gondii* in brain cells. *BMC Genomics* 20, 705. 10.1186/s12864-019-6076-4.
86. Casl, M.T., Bulatovic, G., Orlic, P., and Sabljari-Matovinovic, M. (1995). The diagnostic capacity of serum amyloid A protein for early recognition of kidney allograft rejection. *Nephrol Dial Transplant* 10, 1901-1904.

87. Casl, M.T., Coen, D., and Simic, D. (1996). Serum amyloid A protein in the prediction of postburn complications and fatal outcome in patients with severe burns. *Eur J Clin Chem Clin Biochem* 34, 31-35. 10.1515/cclm.1996.34.1.31.
88. Jang, S.Y., Shin, Y.K., Lee, H.Y., Park, J.Y., Suh, D.J., Kim, J.K., Bae, Y.S., and Park, H.T. (2012). Local production of serum amyloid a is implicated in the induction of macrophage chemoattractants in Schwann cells during wallerian degeneration of peripheral nerves. *Glia* 60, 1619-1628. 10.1002/glia.22382.
89. Ren, S.W., Qi, X., Jia, C.K., and Wang, Y.Q. (2014). Serum amyloid A and pairing formyl peptide receptor 2 are expressed in corneas and involved in inflammation-mediated neovascularization. *Int J Ophthalmol* 7, 187-193. 10.3980/j.issn.2222-3959.2014.02.01.
90. Gonzalez-Pena, D., Nixon, S.E., O'Connor, J.C., Southey, B.R., Lawson, M.A., McCusker, R.H., Borrás, T., Machuca, D., Hernandez, A.G., Dantzer, R., et al. (2016). Microglia Transcriptome Changes in a Model of Depressive Behavior after Immune Challenge. *PLoS One* 11, e0150858. 10.1371/journal.pone.0150858.
91. Luis, C.A., Abdullah, L., Ait-Ghezala, G., Mouzon, B., Keegan, A.P., Crawford, F., and Mullan, M. (2011). Feasibility of Predicting MCI/AD Using Neuropsychological Tests and Serum beta-Amyloid. *Int J Alzheimers Dis* 2011, 786264. 10.4061/2011/786264.
92. Luis, C.A., Abdullah, L., Paris, D., Quadros, A., Mullan, M., Mouzon, B., Ait-Ghezala, G., Crawford, F., and Mullan, M. (2009). Serum beta-amyloid correlates with neuropsychological impairment. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 16, 203-218. 10.1080/13825580802411766.
93. de Oliveira, E.M., Visniauskas, B., Tufik, S., Andersen, M.L., Chagas, J.R., and Campa, A. (2017). Serum Amyloid A Production Is Triggered by Sleep Deprivation in Mice and Humans: Is That the Link between Sleep Loss and Associated Comorbidities? *Nutrients* 9. 10.3390/nu9030311.
94. Connolly, M., Marrelli, A., Blades, M., McCormick, J., Maderia, P., Godson, C., Mullan, R., FitzGerald, O., Bresnihan, B., Pitzalis, C., et al. (2010). Acute serum amyloid A induces migration, angiogenesis, and inflammation in synovial cells in vitro and in a human rheumatoid arthritis/SCID mouse chimera model. *J Immunol* 184, 6427-6437. 10.4049/jimmunol.0902941.
95. Connolly, M., Mullan, R.H., McCormick, J., Matthews, C., Sullivan, O., Kennedy, A., FitzGerald, O., Poole, A.R., Bresnihan, B., Veale, D.J., and Fearon, U. (2012). Acute-phase serum amyloid A regulates tumor necrosis factor alpha and matrix turnover and predicts disease progression in patients with inflammatory arthritis before and after biologic therapy. *Arthritis Rheum* 64, 1035-1045. 10.1002/art.33455.
96. Geurts, J., Joosten, L.A., Takahashi, N., Arntz, O.J., Gluck, A., Bennink, M.B., van den Berg, W.B., and van de Loo, F.A. (2009). Computational design and application of endogenous promoters for transcriptionally targeted gene therapy for rheumatoid arthritis. *Mol Ther* 17, 1877-1887. 10.1038/mt.2009.182.
97. Geurts, J., Vermeij, E.A., Pohlers, D., Arntz, O.J., Kinne, R.W., van den Berg, W.B., and van de Loo, F.A. (2011). A novel Saa3-promoter reporter distinguishes inflammatory subtypes in experimental arthritis and human synovial fibroblasts. *Ann Rheum Dis* 70, 1311-1319. 10.1136/ard.2010.135665.
98. Mullan, R.H., Bresnihan, B., Golden-Mason, L., Markham, T., O'Hara, R., FitzGerald, O., Veale, D.J., and Fearon, U. (2006). Acute-phase serum amyloid A stimulation of angiogenesis, leukocyte recruitment, and matrix degradation in rheumatoid arthritis through an NF-kappaB-dependent signal transduction pathway. *Arthritis Rheum* 54, 105-114. 10.1002/art.21518.
99. Saha, A., Chopra, Y., Theis, J.D., Vrana, J.A., and Sethi, S. (2013). AA amyloidosis associated with systemic-onset juvenile idiopathic arthritis. *Am J Kidney Dis* 62, 834-838. 10.1053/j.ajkd.2013.02.377.
100. Soric Hosman, I., Kos, I., and Lamot, L. (2020). Serum Amyloid A in Inflammatory Rheumatic Diseases: A Compendious Review of a Renowned Biomarker. *Front Immunol* 11, 631299. 10.3389/fimmu.2020.631299.
101. Vallon, R., Freuler, F., Desta-Tsedu, N., Robeva, A., Dawson, J., Wenner, P., Engelhardt, P., Boes, L., Schnyder, J., Tschopp, C., et al. (2001). Serum amyloid A (apoSAA) expression is up-regulated in rheumatoid arthritis and induces transcription of matrix metalloproteinases. *J Immunol* 166, 2801-2807. 10.4049/jimmunol.166.4.2801.
102. Yoo, J., Lee, S.K., Lim, M., Sheen, D., Choi, E.H., and Kim, S.A. (2017). Exosomal amyloid A and lymphatic vessel endothelial hyaluronin acid receptor-1 proteins are associated with disease activity in rheumatoid arthritis. *Arthritis Res Ther* 19, 119. 10.1186/s13075-017-1334-9.

103. Jin, S., Wang, Y., Qie, C., Yang, L., Wu, Y., Zhang, T., Di, J., and Liu, J. (2022). Single-Cell RNA Sequencing Reveals the Immune Cell Profiling in IMQ Induced Psoriasis-Like Model. *J Inflamm Res* 15, 5999-6012. 10.2147/JIR.S379349.
104. Davis, T.A., Conradie, D., Shridas, P., de Beer, F.C., Engelbrecht, A.M., and de Villiers, W.J.S. (2021). Serum Amyloid A Promotes Inflammation-Associated Damage and Tumorigenesis in a Mouse Model of Colitis-Associated Cancer. *Cell Mol Gastroenterol Hepatol* 12, 1329-1341. 10.1016/j.jcmgh.2021.06.016.
105. Djurec, M., Grana, O., Lee, A., Troule, K., Espinet, E., Cabras, L., Navas, C., Blasco, M.T., Martin-Diaz, L., Burdiel, M., et al. (2018). Saa3 is a key mediator of the protumorigenic properties of cancer-associated fibroblasts in pancreatic tumors. *Proc Natl Acad Sci U S A* 115, E1147-E1156. 10.1073/pnas.1717802115.
106. Lee, J.M., Kim, E.K., Seo, H., Jeon, I., Chae, M.J., Park, Y.J., Song, B., Kim, Y.S., Kim, Y.J., Ko, H.J., and Kang, C.Y. (2014). Serum amyloid A3 exacerbates cancer by enhancing the suppressive capacity of myeloid-derived suppressor cells via TLR2-dependent STAT3 activation. *Eur J Immunol* 44, 1672-1684. 10.1002/eji.201343867.
107. Zhang, C., Li, Q., Xu, Q., Dong, W., Li, C., Deng, B., Gong, J., Zhang, L.Z., and Jin, J. (2023). Pulmonary interleukin 1 beta/serum amyloid A3 axis promotes lung metastasis of hepatocellular carcinoma by facilitating the pre-metastatic niche formation. *J Exp Clin Cancer Res* 42, 166. 10.1186/s13046-023-02748-4.
108. Lee, J.Y., Hall, J.A., Kroehling, L., Wu, L., Najar, T., Nguyen, H.H., Lin, W.Y., Yeung, S.T., Silva, H.M., Li, D., et al. (2020). Serum Amyloid A Proteins Induce Pathogenic Th17 Cells and Promote Inflammatory Disease. *Cell* 183, 2036-2039. 10.1016/j.cell.2020.12.008.
109. Reigstad, C.S., Lunden, G.O., Felin, J., and Backhed, F. (2009). Regulation of serum amyloid A3 (SAA3) in mouse colonic epithelium and adipose tissue by the intestinal microbiota. *PLoS One* 4, e5842. 10.1371/journal.pone.0005842.
110. Han, C.Y., Subramanian, S., Chan, C.K., Omer, M., Chiba, T., Wight, T.N., and Chait, A. (2007). Adipocyte-derived serum amyloid A3 and hyaluronan play a role in monocyte recruitment and adhesion. *Diabetes* 56, 2260-2273. 10.2337/db07-0218.
111. Jahangiri, A., Wilson, P.G., Hou, T., Brown, A., King, V.L., and Tannock, L.R. (2013). Serum amyloid A is found on ApoB-containing lipoproteins in obese humans with diabetes. *Obesity (Silver Spring)* 21, 993-996. 10.1002/oby.20126.
112. Ji, A., Trumbauer, A.C., Noffsinger, V.P., Jeon, H., Patrick, A.C., De Beer, F.C., Webb, N.R., Tannock, L.R., and Shridas, P. (2022). Serum Amyloid A is not obligatory for high-fat, high-sucrose, cholesterol-fed diet-induced obesity and its metabolic and inflammatory complications. *PLoS One* 17, e0266688. 10.1371/journal.pone.0266688.
113. Sanada, Y., Yamamoto, T., Satake, R., Yamashita, A., Kanai, S., Kato, N., van de Loo, F.A., Nishimura, F., Scherer, P.E., and Yanaka, N. (2016). Serum Amyloid A3 Gene Expression in Adipocytes is an Indicator of the Interaction with Macrophages. *Sci Rep* 6, 38697. 10.1038/srep38697.
114. Scheja, L., Heese, B., Zitzer, H., Michael, M.D., Siesky, A.M., Pospisil, H., Beisiegel, U., and Seedorf, K. (2008). Acute-phase serum amyloid A as a marker of insulin resistance in mice. *Exp Diabetes Res* 2008, 230837. 10.1155/2008/230837.
115. Chen, A., Wang, Y., Wu, J., Tang, D., Zhu, Q., Lu, A., Yang, J., Cai, Z., and Shi, J. (2020). Identification and characterization of dynamically regulated hepatitis-related genes in a concanavalin A-induced liver injury model. *Aging (Albany NY)* 12, 23187-23199. 10.18632/aging.104089.
116. Siegmund, S.V., Schlosser, M., Schildberg, F.A., Seki, E., De Minicis, S., Uchinami, H., Kuntzen, C., Knolle, P.A., Strassburg, C.P., and Schwabe, R.F. (2016). Serum Amyloid A Induces Inflammation, Proliferation and Cell Death in Activated Hepatic Stellate Cells. *PLoS One* 11, e0150893. 10.1371/journal.pone.0150893.
117. Ji, A., Trumbauer, A.C., Noffsinger, V.P., Meredith, L.W., Dong, B., Wang, Q., Guo, L., Li, X., De Beer, F.C., Webb, N.R., et al. (2023). Deficiency of Acute-Phase Serum Amyloid A Exacerbates Sepsis-Induced Mortality and Lung Injury in Mice. *Int J Mol Sci* 24. 10.3390/ijms242417501.
118. Kawasaki, H., Murakami, T., Badr, Y., Kamiya, S., Shimizu, K., Okada, A., and Inoshima, Y. (2020). In vitro and ex vivo expression of serum amyloid A3 in mouse lung epithelia. *Exp Lung Res* 46, 352-361. 10.1080/01902148.2020.1809750.

119. Christophersen, D.V., Moller, P., Thomsen, M.B., Lykkesfeldt, J., Loft, S., Wallin, H., Vogel, U., and Jacobsen, N.R. (2021). Accelerated atherosclerosis caused by serum amyloid A response in lungs of ApoE(-/-) mice. *FASEB J* 35, e21307. 10.1096/fj.202002017R.
120. Dieter, B.P., Meek, R.L., Anderberg, R.J., Cooney, S.K., Bergin, J.L., Zhang, H., Nair, V., Kretzler, M., Brosius, F.C., and Tuttle, K.R. (2019). Serum amyloid A and Janus kinase 2 in a mouse model of diabetic kidney disease. *PLoS One* 14, e0211555. 10.1371/journal.pone.0211555.
121. Saliu, T.P., Yazawa, N., Hashimoto, K., Miyata, K., Kudo, A., Horii, M., Kamesawa, M., Kumrungsee, T., and Yanaka, N. (2022). Serum Amyloid A3 Promoter-Driven Luciferase Activity Enables Visualization of Diabetic Kidney Disease. *Int J Mol Sci* 23. 10.3390/ijms23020899.
122. Kumrungsee, T., Kariya, T., Hashimoto, K., Koyano, T., Yazawa, N., Hashimoto, T., Sanada, Y., Matsuyama, M., Sotomaru, Y., Sakurai, H., et al. (2019). The serum amyloid A3 promoter-driven luciferase reporter mice is a valuable tool to image early renal fibrosis development and shows the therapeutic effect of glucosyl-hesperidin treatment. *Sci Rep* 9, 14101. 10.1038/s41598-019-50685-0.
123. Thaler, R., Zwerina, J., Rumpler, M., Spitzer, S., Gamsjaeger, S., Paschalis, E.P., Klaushofer, K., and Varga, F. (2013). Homocysteine induces serum amyloid A3 in osteoblasts via unlocking RGD-motifs in collagen. *FASEB J* 27, 446-463. 10.1096/fj.12-208058.
124. Crookenden, M.A., Lake, A.V.R., Burke, C.R., Pratt, J.T., Mitchell, M.D., Phyn, C.V.C., Roche, J.R., and Heiser, A. (2023). Effect of nonsteroidal anti-inflammatory drugs on the inflammatory response of bovine endometrial epithelial cells in vitro. *J Dairy Sci* 106, 2651-2666. 10.3168/jds.2021-21742.