

REFERENCES

- Aguilar-Cazares, D., Chavez-Dominguez, R., Carlos-Reyes, A., Lopez-Camarillo, C., Hernadez de la Cruz, O. N., & Lopez-Gonzalez, J. S. (2019). Contribution of Angiogenesis to Inflammation and Cancer. *Frontiers in Oncology*, 9. <https://doi.org/10.3389/fonc.2019.01399>
- Amer, R., Tiosano, L., & Pe'er, J. (2018). Leucine-Rich α -2-Glycoprotein-1 (LRG-1) Expression in Retinoblastoma. *Investigative Ophthalmology & Visual Science*, 59(2), 685. <https://doi.org/10.1167/iovs.17-22785>
- Ban, Z., He, J., Tang, Z., Zhang, L., & Xu, Z. (2019). LRG-1 enhances the migration of thyroid carcinoma cells through promotion of the epithelial-mesenchymal transition by activating MAPK/p38 signaling. *Oncology Reports*. <https://doi.org/10.3892/or.2019.7123>
- Banks, A. S., McAllister, F. E., Camporez, J. P. G., Zushin, P.-J. H., Jurczak, M. J., Laznik-Bogoslavski, D., Shulman, G. I., Gygi, S. P., & Spiegelman, B. M. (2014). An ERK/Cdk5 axis controls the diabetogenic actions of PPAR γ . *Nature*, 517(7534), 391–395. <https://doi.org/10.1038/nature13887>
- Bettini, S., Favaretto, F., Compagnin, C., Belligoli, A., Sanna, M., Fabris, R., Serra, R., Dal Prà, C., Prevedello, L., Foletto, M., Vettor, R., Milan, G., & Busetto, L. (2019). Resting Energy Expenditure, Insulin Resistance and UCP1 Expression in Human Subcutaneous and Visceral Adipose Tissue of Patients With Obesity. *Frontiers in Endocrinology*, 10. <https://doi.org/10.3389/fendo.2019.00548>
- Blüher, M. (2019). Obesity: global epidemiology and pathogenesis. *Nature Reviews Endocrinology*, 15(5), 288–298. <https://doi.org/10.1038/s41574-019-0176-8>
- Boström, P., Wu, J., Jedrychowski, M. P., Korde, A., Ye, L., Lo, J. C., Rasbach, K. A., Boström, E. A., Choi, J. H., Long, J. Z., Kajimura, S., Zingaretti, M. C., Vind, B. F., Tu, H., Cinti, S., Højlund, K., Gygi, S. P., & Spiegelman, B. M. (2012). A PGC1- α -dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*, 481(7382), 463–468. <https://doi.org/10.1038/nature10777>
- Bryda, E. C. (2013). The Mighty Mouse: the impact of rodents on advances in biomedical research. *Missouri Medicine*, 110(3), 207–211. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3987984/>
- Camaré, C., Pucelle, M., Nègre-Salvayre, A., & Salvayre, R. (2017). Angiogenesis in the atherosclerotic plaque. *Redox Biology*, 12, 18–34. <https://doi.org/10.1016/j.redox.2017.01.007>
- Campa, C., Costagliola, C., Incorvaia, C., Sheridan, C., Semeraro, F., De Nadai, K., Sebastiani, A., & Parmeggiani, F. (2010). Inflammatory Mediators and Angiogenic Factors in Choroidal Neovascularization: Pathogenetic Interactions and Therapeutic Implications. *Mediators of Inflammation*, 2010, 1–14. <https://doi.org/10.1155/2010/546826>
- Cannon, B., & Nedergaard, J. (2004). Brown Adipose Tissue: Function and Physiological Significance. *Physiological Reviews*, 84(1), 277–359. <https://doi.org/10.1152/physrev.00015.2003>
- Cao, R., Brakenhielm, E., Wahlestedt, C., Thyberg, J., & Cao, Y. (2001). Leptin induces vascular permeability and synergistically stimulates angiogenesis with FGF-2 and VEGF. *Proceedings of the National Academy of Sciences of the United States of America*, 98(11), 6390–6395.

<https://doi.org/10.1073/pnas.101564798>

Choe, S. S., Huh, J. Y., Hwang, I. J., Kim, J. I., & Kim, J. B. (2016). Adipose Tissue Remodeling: Its Role in Energy Metabolism and Metabolic Disorders. *Frontiers in Endocrinology*, 7. <https://doi.org/10.3389/fendo.2016.00030>

Choi, J. H., Banks, A. S., Estall, J. L., Kajimura, S., Boström, P., Laznik, D., Ruas, J. L., Chalmers, M. J., Kamenecka, T. M., Blüher, M., Griffin, P. R., & Spiegelman, B. M. (2010). Anti-diabetic drugs inhibit obesity-linked phosphorylation of PPAR γ by Cdk5. *Nature*, 466(7305), 451–456. <https://doi.org/10.1038/nature09291>

Chong, P. F., Sakai, Y., Torisu, H., Tanaka, T., Furuno, K., Mizuno, Y., Ohga, S., Hara, T., & Kira, R. (2018). Leucine-rich alpha-2 glycoprotein in the cerebrospinal fluid is a potential inflammatory biomarker for meningitis. *Journal of the Neurological Sciences*, 392, 51–55. <https://doi.org/10.1016/j.jns.2018.07.006>

Chooi, Y. C., Ding, C., & Magkos, F. (2019). The epidemiology of obesity. *Metabolism*, 92, 6–10. <https://doi.org/10.1016/j.metabol.2018.09.005>

Chun, T. H., Inoue, M., Morisaki, H., Yamanaka, I., Miyamoto, Y., Okamura, T., Sato-Kusubata, K., & Weiss, S. J. (2010). Genetic Link Between Obesity and MMP14-Dependent Adipogenic Collagen Turnover. *Diabetes*, 59(10), 2484–2494. <https://doi.org/10.2337/db10-0073>

Cinti, S., Mitchell, G., Barbatelli, G., Murano, I., Ceresi, E., Faloia, E., Wang, S., Fortier, M., Greenberg, A. S., & Obin, M. S. (2005). Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. *Journal of Lipid Research*, 46(11), 2347–2355. <https://doi.org/10.1194/jlr.m500294-jlr200>

Clément, K., Vaisse, C., Lahlou, N., Cabrol, S., Pelloux, V., Cassuto, D., Gourmelen, M., Dina, C., Chambaz, J., Lacorte, J. M., Basdevant, A., Bougnères, P., Lebouc, Y., Froguel, P., & Guy-Grand, B. (1998). A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature*, 392(6674), 398–401. <https://doi.org/10.1038/32911>

Codina, R., Vanasse, A., Kelekar, A., Vezys, V., & Jemmerson, R. (2009). Cytochrome c-induced lymphocyte death from the outside in: inhibition by serum leucine-rich alpha-2-glycoprotein-1. *Apoptosis*, 15(2), 139–152. <https://doi.org/10.1007/s10495-009-0412-0>

Crewe, C., An, Y. A., & Scherer, P. E. (2017). The ominous triad of adipose tissue dysfunction: inflammation, fibrosis, and impaired angiogenesis. *Journal of Clinical Investigation*, 127(1), 74–82. <https://doi.org/10.1172/jci88883>

Dalmas, E., Toubal, A., Alzaid, F., Blazek, K., Eames, H. L., Lebozec, K., Pini, M., Hainault, I., Montastier, E., Denis, R. G. P., Ancel, P., Lacombe, A., Ling, Y., Allatif, O., Cruciani-Guglielmiacci, C., André, S., Viguerie, N., Poitou, C., Stich, V., ... Venteclef, N. (2015). Irf5 deficiency in macrophages promotes beneficial adipose tissue expansion and insulin sensitivity during obesity. *Nature Medicine*, 21(6), 610–618. <https://doi.org/10.1038/nm.3829>

Datta, R., Podolsky, M. J., & Atabai, K. (2018). Fat fibrosis: friend or foe? *JCI Insight*, 3(19). <https://doi.org/10.1172/jci.insight.122289>

Di Prospero, N. A., Artis, E., Andrade-Gordon, P., Johnson, D. L., Vaccaro, N., Xi, L., & Rothenberg, P. (2014). CCR2 antagonism in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. *Diabetes, Obesity and Metabolism*, 16(11), 1055–1064. <https://doi.org/10.1111/dom.12309>

- Divoux, A., & Clément, K. (2011). Architecture and the extracellular matrix: the still unappreciated components of the adipose tissue. *Obesity Reviews*, 12(5), e494–e503. <https://doi.org/10.1111/j.1467-789x.2010.00811.x>
- Dominguez, H., Storgaard, H., Rask-Madsen, C., Steffen Hermann, T., Ihlemann, N., Baunbjerg Nielsen, D., Spohr, C., Kober, L., Vaag, A., & Torp-Pedersen, C. (2005). Metabolic and Vascular Effects of Tumor Necrosis Factor- α Blockade with Etanercept in Obese Patients with Type 2 Diabetes. *Journal of Vascular Research*, 42(6), 517–525. <https://doi.org/10.1159/000088261>
- Enkhbayar, P., Kamiya, M., Osaki, M., Matsumoto, T., & Matsushima, N. (2003). Structural principles of leucine-rich repeat (LRR) proteins. *Proteins: Structure, Function, and Bioinformatics*, 54(3), 394–403. <https://doi.org/10.1002/prot.10605>
- Evans, R. M., Barish, G. D., & Wang, Y.-X. (2004). PPARs and the complex journey to obesity. *Nature Medicine*, 10(4), 355–361. <https://doi.org/10.1038/nm1025>
- Exley, M. A., Hand, L., O'Shea, D., & Lynch, L. (2014). Interplay between the immune system and adipose tissue in obesity. *Journal of Endocrinology*, 223(2), R41–R48. <https://doi.org/10.1530/joe-13-0516>
- Farooqi, I. S., Yeo, G. S., Keogh, J. M., Aminian, S., Jebb, S. A., Butler, G., Cheetham, T., & O'Rahilly, S. (2000). Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency. *The Journal of Clinical Investigation*, 106(2), 271–279. <https://doi.org/10.1172/JCI9397>
- Feingold, K. R., & Grunfeld, C. (2018, April 10). *Obesity and Dyslipidemia*. Nih.Gov; MDText.com, Inc. <https://www.ncbi.nlm.nih.gov/books/NBK305895/>
- Feuerer, M., Herrero, L., Cipolletta, D., Naaz, A., Wong, J., Nayer, A., Lee, J., Goldfine, A. B., Benoist, C., Shoelson, S., & Mathis, D. (2009). Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. *Nature Medicine*, 15(8), 930–939. <https://doi.org/10.1038/nm.2002>
- Friedlander, M. (2007). Fibrosis and diseases of the eye. *The Journal of Clinical Investigation*, 117(3), 576–586. <https://doi.org/10.1172/JCI31030>
- García-Ruiz, E., Reynés, B., Díaz-Rúa, R., Ceresi, E., Oliver, P., & Palou, A. (2015). The intake of high-fat diets induces the acquisition of brown adipocyte gene expression features in white adipose tissue. *International Journal of Obesity*, 39(11), 1619–1629. <https://doi.org/10.1038/ijo.2015.112>
- GBD 2015 Obesity Collaborators. (2017). Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *New England Journal of Medicine*, 377(1), 13–27. <https://doi.org/10.1056/nejmoa1614362>
- Ghaben, A. L., & Scherer, P. E. (2019). Adipogenesis and metabolic health. *Nature Reviews Molecular Cell Biology*, 20(4), 242–258. <https://doi.org/10.1038/s41580-018-0093-z>
- Ghorbani, M., & Himms-Hagen, J. (1997). Appearance of brown adipocytes in white adipose tissue during CL 316,243-induced reversal of obesity and diabetes in Zucker fa/fa rats. *International Journal of Obesity*, 21(6), 465–475.
- Haczeyni, F., Bell-Anderson, K. S., & Farrell, G. C. (2017). Causes and mechanisms of adipocyte enlargement and adipose expansion. *Obesity Reviews*, 19(3), 406–420. <https://doi.org/10.1111/obr.12646>

- Haupt, H., & Baudner, S. (1977). [Isolation and characterization of an unknown, leucine-rich 3.1-S-alpha2-glycoprotein from human serum (author's transl)]. *Hoppe-Seyler's Zeitschrift Fur Physiologische Chemie*, 358(6), 639–646.
- Henriques, F., H. Bedard, A., & Luiz Batista Júnior, M. (2019). Adipose Tissue Inflammation and Metabolic Disorders. *InTechOpen*. <https://doi.org/10.5772/intechopen.88631>
- Heymsfield, S. B., & Wadden, T. A. (2017). Mechanisms, Pathophysiology, and Management of Obesity. *New England Journal of Medicine*, 376(3), 254–266. <https://doi.org/10.1056/nejmra1514009>
- Honda, H., Fujimoto, M., Serada, S., Urushima, H., Mishima, T., Lee, H., Ohkawara, T., Kohno, N., Hattori, N., Yokoyama, A., & Naka, T. (2017). Leucine-rich α -2 glycoprotein promotes lung fibrosis by modulating TGF- β signaling in fibroblasts. *Physiological Reports*, 5(24), e13556. <https://doi.org/10.14814/phy2.13556>
- Hotamisligil, G., Shargill, N., & Spiegelman, B. (1993). Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science*, 259(5091), 87–91. <https://doi.org/10.1126/science.7678183>
- Hruby, A., & Hu, F. B. (2014). The Epidemiology of Obesity: A Big Picture. *PharmacoEconomics*, 33(7), 673–689. <https://doi.org/10.1007/s40273-014-0243-x>
- Hruby, A., Manson, J. E., Qi, L., Malik, V. S., Rimm, E. B., Sun, Q., Willett, W. C., & Hu, F. B. (2016). Determinants and Consequences of Obesity. *American Journal of Public Health*, 106(9), 1656–1662. <https://doi.org/10.2105/ajph.2016.303326>
- Iwayama, T., Steele, C., Yao, L., Dozmorov, M. G., Karamichos, D., Wren, J. D., & Olson, L. E. (2015). PDGFR α signaling drives adipose tissue fibrosis by targeting progenitor cell plasticity. *Genes & Development*, 29(11), 1106–1119. <https://doi.org/10.1101/gad.260554.115>
- Juge-Aubry, C. E., Henrichot, E., & Meier, C. A. (2005). Adipose tissue: a regulator of inflammation. *Best Practice & Research Clinical Endocrinology & Metabolism*, 19(4), 547–566. <https://doi.org/10.1016/j.beem.2005.07.009>
- Keophiphath, M., Achard, V., Henegar, C., Rouault, C., Clément, K., & Lacasa, D. (2009). Macrophage-Secreted Factors Promote a Profibrotic Phenotype in Human Preadipocytes. *Molecular Endocrinology*, 23(1), 11–24. <https://doi.org/10.1210/me.2008-0183>
- Kern, L., Mittenbühler, M., Vesting, A., Ostermann, A., Wunderlich, C., & Wunderlich, F. (2018). Obesity-Induced TNF α and IL-6 Signaling: The Missing Link between Obesity and Inflammation—Driven Liver and Colorectal Cancers. *Cancers*, 11(1), 24. <https://doi.org/10.3390/cancers11010024>
- Khan, T., Muise, E. S., Iyengar, P., Wang, Z. V., Chandalia, M., Abate, N., Zhang, B. B., Bonaldo, P., Chua, S., & Scherer, P. E. (2008). Metabolic Dysregulation and Adipose Tissue Fibrosis: Role of Collagen VI. *Molecular and Cellular Biology*, 29(6), 1575–1591. <https://doi.org/10.1128/mcb.01300-08>
- Klop, B., Elte, J., & Cabezas, M. (2013). Dyslipidemia in Obesity: Mechanisms and Potential Targets. *Nutrients*, 5(4), 1218–1240. <https://doi.org/10.3390/nu5041218>
- Krude, H., Biebermann, H., Luck, W., Horn, R., Brabant, G., & Grütters, A. (1998). Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nature Genetics*, 19(2), 155–157. <https://doi.org/10.1038/509>

- Kusminski, C. M., Bickel, P. E., & Scherer, P. E. (2016). Targeting adipose tissue in the treatment of obesity-associated diabetes. *Nature Reviews Drug Discovery*, 15(9), 639–660. <https://doi.org/10.1038/nrd.2016.75>
- Lee, H. P., Lin, C. Y., Shih, J. S., Fong, Y. C., Wang, S. W., Li, T. M., & Tang, C. H. (2015). Adiponectin promotes VEGF-A-dependent angiogenesis in human chondrosarcoma through PI3K, Akt, mTOR, and HIF- α pathway. *Oncotarget*, 6(34), 36746–36761. <https://doi.org/10.18632/oncotarget.5479>
- Lim, J., Park, H. S., Kim, J., Jang, Y. J., Kim, J.-H., Lee, Y., & Heo, Y. (2020). Depot-specific UCP1 expression in human white adipose tissue and its association with obesity-related markers. *International Journal of Obesity*, 44(3), 697–706. <https://doi.org/10.1038/s41366-020-0528-4>
- Lin, D., Chun, T.-H., & Kang, L. (2016). Adipose extracellular matrix remodelling in obesity and insulin resistance. *Biochemical Pharmacology*, 119, 8–16. <https://doi.org/10.1016/j.bcp.2016.05.005>
- Liu, C., Lim, S. T., Teo, M. H. Y., Tan, M. S. Y., Kulkarni, M. D., Qiu, B., Li, A., Lal, S., dos Remedios, C. G., Tan, N. S., Wahli, W., Ferenczi, M. A., Song, W., Hong, W., & Wang, X. (2019). Collaborative Regulation of LRG1 by TGF- β 1 and PPAR- β/δ Modulates Chronic Pressure Overload-Induced Cardiac Fibrosis. *Circulation: Heart Failure*, 12(12). <https://doi.org/10.1161/circheartfailure.119.005962>
- Lo, K. A., & Sun, L. (2013). Turning WAT into BAT: a review on regulators controlling the browning of white adipocytes. *Bioscience Reports*, 33(5). <https://doi.org/10.1042/bsr20130046>
- Longo, M., Zatterale, F., Naderi, J., Parrillo, L., Formisano, P., Raciti, G. A., Beguinot, F., & Miele, C. (2019). Adipose Tissue Dysfunction as Determinant of Obesity-Associated Metabolic Complications. *International Journal of Molecular Sciences*, 20(9), 2358. <https://doi.org/10.3390/ijms20092358>
- Lumeng, C. N., Bodzin, J. L., & Saltiel, A. R. (2007). Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *Journal of Clinical Investigation*, 117(1), 175–184. <https://doi.org/10.1172/jci29881>
- MacDonald, I., Liu, S.-C., Su, C.-M., Wang, Y.-H., Tsai, C.-H., & Tang, C.-H. (2018). Implications of Angiogenesis Involvement in Arthritis. *International Journal of Molecular Sciences*, 19(7), 2012. <https://doi.org/10.3390/ijms19072012>
- Marieb, E. N., & Hoehn, K. (2013). *Human anatomy and physiology*. Pearson.
- Marseglia, L., Manti, S., D'Angelo, G., Nicotera, A., Parisi, E., Di Rosa, G., Gitto, E., & Arrigo, T. (2014). Oxidative Stress in Obesity: A Critical Component in Human Diseases. *International Journal of Molecular Sciences*, 16(1), 378–400. <https://doi.org/10.3390/ijms16010378>
- Martinez-Santibañez, G. (2015). *Insights on adipose tissue extracellular matrix remodeling: Models of diet-induced obesity and weight loss* [Doctor of Philosophy Dissertation]. <https://deepblue.lib.umich.edu/handle/2027.42/113435>
- Matafome, P., & Seiça, R. (2017). Function and Dysfunction of Adipose Tissue. *Advances in Neurobiology*, 3–31. https://doi.org/10.1007/978-3-319-63260-5_1
- Mauer, J., Chaurasia, B., Goldau, J., Vogt, M. C., Ruud, J., Nguyen, K. D., Theurich, S., Hausen, A. C., Schmitz, J., Brönnike, H. S., Estevez, E., Allen, T. L., Mesaros, A., Partridge, L., Febbraio, M. A., Chawla, A., Wunderlich, F. T., & Brüning, J. C. (2014). Signaling by IL-6 promotes alternative

activation of macrophages to limit endotoxemia and obesity-associated resistance to insulin. *Nature Immunology*, 15(5), 423–430. <https://doi.org/10.1038/ni.2865>

Mekary, R. A., Feskanich, D., Malspeis, S., Hu, F. B., Willett, W. C., & Field, A. E. (2009). Physical activity patterns and prevention of weight gain in premenopausal women. *International Journal of Obesity*, 33(9), 1039–1047. <https://doi.org/10.1038/ijo.2009.127>

Montague, C. T., Farooqi, I. S., Whitehead, J. P., Soos, M. A., Rau, H., Wareham, N. J., Sewter, C. P., Digby, J. E., Mohammed, S. N., Hurst, J. A., Cheetham, C. H., Earley, A. R., Barnett, A. H., Prins, J. B., & O’Rahilly, S. (1997). Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature*, 387(6636), 903–908. <https://doi.org/10.1038/43185>

Ng, A. C. Y., Eisenberg, J. M., Heath, R. J. W., Huett, A., Robinson, C. M., Nau, G. J., & Xavier, R. J. (2010). Human leucine-rich repeat proteins: a genome-wide bioinformatic categorization and functional analysis in innate immunity. *Proceedings of the National Academy of Sciences*, 108(Supplement_1), 4631–4638. <https://doi.org/10.1073/pnas.1000093107>

Nishizawa, H., & Shimomura, I. (2018). Fat cell lipolysis and future weight gain. *Journal of Diabetes Investigation*, 10(2), 221–223. <https://doi.org/10.1111/jdi.12950>

Ofei, F. (2005). Obesity - a preventable disease. *Ghana Medical Journal*, 39(3), 98–101. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1790820/>

Palazon, A., Goldrath, A. W., Nizet, V., & Johnson, R. S. (2014). HIF Transcription Factors, Inflammation, and Immunity. *Immunity*, 41(4), 518–528. <https://doi.org/10.1016/j.jimmuni.2014.09.008>

Panuganti, K. K., Nguyen, M., & Kshirsagar, R. K. (2019, October 28). *Obesity*. Nih.Gov; StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK459357/>

Pasarica, M., Sereda, O. R., Redman, L. M., Albarado, D. C., Hymel, D. T., Roan, L. E., Rood, J. C., Burk, D. H., & Smith, S. R. (2009). Reduced Adipose Tissue Oxygenation in Human Obesity: Evidence for Rarefaction, Macrophage Chemotaxis, and Inflammation Without an Angiogenic Response. *Diabetes*, 58(3), 718–725. <https://doi.org/10.2337/db08-1098>

Pek, S. L. T., Cheng, A. K. S., Lin, M. X., Wong, M. S., Chan, E. Z. L., Moh, A. M. C., Sum, C. F., Lim, S. C., & Tavintharan, S. (2018). Association of circulating proinflammatory marker, leucine-rich- α 2-glycoprotein (LRG1), following metabolic/bariatric surgery. *Diabetes/Metabolism Research and Reviews*, 34(7), e3029. <https://doi.org/10.1002/dmrr.3029>

Pek, S. L. T., Tavintharan, S., Wang, X., Lim, S. C., Woon, K., Yeoh, L. Y., Ng, X., Liu, J., & Sum, C. F. (2015). Elevation of a Novel Angiogenic Factor, Leucine-Rich- α 2-Glycoprotein (LRG1), Is Associated With Arterial Stiffness, Endothelial Dysfunction, and Peripheral Arterial Disease in Patients With Type 2 Diabetes. *The Journal of Clinical Endocrinology & Metabolism*, 100(4), 1586–1593. <https://doi.org/10.1210/jc.2014-3855>

Puigserver, P., Wu, Z., Park, C. W., Graves, R., Wright, M., & Spiegelman, B. M. (1998). A Cold-Inducible Coactivator of Nuclear Receptors Linked to Adaptive Thermogenesis. *Cell*, 92(6), 829–839. [https://doi.org/10.1016/s0092-8674\(00\)81410-5](https://doi.org/10.1016/s0092-8674(00)81410-5)

Rainer, T., Leung, L., Chan, C., Leung, Y., Cheng, N., Lai, P., Cheung, Y., & Graham, C. (2017). Circulating human leucine-rich α -2-glycoprotein 1 mRNA and protein levels to detect acute appendicitis in patients with acute abdominal pain. *Clinical Biochemistry*, 50(9), 485–490. <https://doi.org/10.1016/j.clinbiochem.2017.02.010>

Ravnskjaer, K., Frigerio, F., Boergesen, M., Nielsen, T., Maechler, P., & Mandrup, S. (2009). PPAR δ is a

fatty acid sensor that enhances mitochondrial oxidation in insulin-secreting cells and protects against fatty acid-induced dysfunction. *Journal of Lipid Research*, 51(6), 1370–1379. <https://doi.org/10.1194/jlr.m001123>

Rotter, V., Nagaev, I., & Smith, U. (2003). Interleukin-6 (IL-6) Induces Insulin Resistance in 3T3-L1 Adipocytes and Is, Like IL-8 and Tumor Necrosis Factor- α , Overexpressed in Human Fat Cells from Insulin-resistant Subjects. *Journal of Biological Chemistry*, 278(46), 45777–45784. <https://doi.org/10.1074/jbc.m301977200>

Ruban, A., Stoenchev, K., Ashrafian, H., & Teare, J. (2019). Current treatments for obesity. *Clinical Medicine*, 19(3), 205–212. <https://doi.org/10.7861/clinmedicine.19-3-205>

Ruiz-Ojeda, F. J., Méndez-Gutiérrez, A., Aguilera, C., & Plaza-Díaz, J. (2019). Extracellular Matrix Remodeling of Adipose Tissue in Obesity and Metabolic Diseases. *International Journal of Molecular Sciences*, 20(19), 4888. <https://doi.org/10.3390/ijms20194888>

Schipper, H. S., Prakken, B., Kalkhoven, E., & Boes, M. (2012). Adipose tissue-resident immune cells: key players in immunometabolism. *Trends in Endocrinology & Metabolism*, 23(8), 407–415. <https://doi.org/10.1016/j.tem.2012.05.011>

Schulze, M. B., Fung, T. T., Manson, J. E., Willett, W. C., & Hu, F. B. (2006). Dietary Patterns and Changes in Body Weight in Women. *Obesity*, 14(8), 1444–1453. <https://doi.org/10.1038/oby.2006.164>

Scroyen, I., Jacobs, F., Cosemans, L., Geest, B. D., & Lijnen, R. (2009). Effect of plasminogen activator inhibitor-1 on adipogenesis in vivo. *Thrombosis and Haemostasis*, 101(02), 388–393. <https://doi.org/10.1160/th08-06-0401>

Seale, P., Conroe, H. M., Estall, J., Kajimura, S., Frontini, A., Ishibashi, J., Cohen, P., Cinti, S., & Spiegelman, B. M. (2011). Prdm16 determines the thermogenic program of subcutaneous white adipose tissue in mice. *Journal of Clinical Investigation*, 121(1), 96–105. <https://doi.org/10.1172/jci44271>

Shimizu, M., Inoue, N., Mizuta, M., Nakagishi, Y., & Yachie, A. (2019). Serum Leucine-Rich α 2-Glycoprotein as a Biomarker for Monitoring Disease Activity in Patients with Systemic Juvenile Idiopathic Arthritis. *Journal of Immunology Research*, 2019, 1–6. <https://doi.org/10.1155/2019/3140204>

Shinzaki, S., Matsuoka, K., Iijima, H., Mizuno, S., Serada, S., Fujimoto, M., Arai, N., Koyama, N., Morii, E., Watanabe, M., Hibi, T., Kanai, T., Takehara, T., & Naka, T. (2016). Leucine-rich Alpha-2 Glycoprotein is a Serum Biomarker of Mucosal Healing in Ulcerative Colitis. *Journal of Crohn's and Colitis*, 11(1), 84–91. <https://doi.org/10.1093/ecco-jcc/jjw132>

Shirai, R., Hirano, F., Ohkura, N., Ikeda, K., & Inoue, S. (2009). Up-regulation of the expression of leucine-rich α 2-glycoprotein in hepatocytes by the mediators of acute-phase response. *Biochemical and Biophysical Research Communications*, 382(4), 776–779. <https://doi.org/10.1016/j.bbrc.2009.03.104>

Sidossis, L., & Kajimura, S. (2015). Brown and beige fat in humans: thermogenic adipocytes that control energy and glucose homeostasis. *Journal of Clinical Investigation*, 125(2), 478–486. <https://doi.org/10.1172/jci78362>

Sng, M. K., Chan, J. S. K., Teo, Z., Phua, T., Tan, E. H. P., Wee, J. W. K., Koh, N. J. N., Tan, C. K., Chen, J. P., Pal, M., Tong, B. M. K., Tnay, Y. L., Ng, X. R., Zhu, P., Chiba, S., Wang, X., Wahli, W., & Tan, N. S. (2018). Selective deletion of PPAR β/δ in fibroblasts causes dermal fibrosis by attenuated LRG1 expression. *Cell Discovery*, 4(1). <https://doi.org/10.1038/s41421-018-0014-5>

- Solomon, D. H. (2011). Association Between Disease-Modifying Antirheumatic Drugs and Diabetes Risk in Patients With Rheumatoid Arthritis and Psoriasis. *JAMA*, 305(24), 2525. <https://doi.org/10.1001/jama.2011.878>
- Song, S., Cheng, J., Yu, B. J., Zhou, L., Xu, H. F., & Yang, L. L. (2020). LRG1 promotes corneal angiogenesis and lymphangiogenesis in a corneal alkali burn mouse model. *International Journal of Ophthalmology*, 13(3), 365–373. <https://doi.org/10.18240/ijo.2020.03.01>
- Srivastava, G., & Apovian, C. M. (2017). Current pharmacotherapy for obesity. *Nature Reviews Endocrinology*, 14(1), 12–24. <https://doi.org/10.1038/nrendo.2017.122>
- Stanley, T. L., Zanni, M. V., Johnsen, S., Rasheed, S., Makimura, H., Lee, H., Khor, V. K., Ahima, R. S., & Grinspoon, S. K. (2011). TNF- α Antagonism with Etanercept Decreases Glucose and Increases the Proportion of High Molecular Weight Adiponectin in Obese Subjects with Features of the Metabolic Syndrome. *The Journal of Clinical Endocrinology & Metabolism*, 96(1), E146–E150. <https://doi.org/10.1210/jc.2010-1170>
- Sun, K., Halberg, N., Khan, M., Magalang, U. J., & Scherer, P. E. (2013). Selective Inhibition of Hypoxia-Inducible Factor 1 Ameliorates Adipose Tissue Dysfunction. *Molecular and Cellular Biology*, 33(5), 904–917. <https://doi.org/10.1128/mcb.00951-12>
- Sun, Kai, Park, J., Gupta, O. T., Holland, W. L., Auerbach, P., Zhang, N., Goncalves Marangoni, R., Nicoloro, S. M., Czech, M. P., Varga, J., Ploug, T., An, Z., & Scherer, P. E. (2014). Endotrophin triggers adipose tissue fibrosis and metabolic dysfunction. *Nature Communications*, 5(1). <https://doi.org/10.1038/ncomms4485>
- Swinburn, B. A., Sacks, G., Hall, K. D., McPherson, K., Finegood, D. T., Moodie, M. L., & Gortmaker, S. L. (2011). The global obesity pandemic: shaped by global drivers and local environments. *The Lancet*, 378(9793), 804–814. [https://doi.org/10.1016/s0140-6736\(11\)60813-1](https://doi.org/10.1016/s0140-6736(11)60813-1)
- Tortora, G. J., & Derrickson, B. H. (2017). *Principles of anatomy & physiology* (15th ed.). Wiley.
- Trayhurn, P., Wang, B., & Wood, I. S. (2008). Hypoxia in adipose tissue: a basis for the dysregulation of tissue function in obesity? *British Journal of Nutrition*, 100(2), 227–235. <https://doi.org/10.1017/s0007114508971282>
- Urushima, H., Fujimoto, M., Mishima, T., Ohkawara, T., Honda, H., Lee, H., Kawahata, H., Serada, S., & Naka, T. (2017). Leucine-rich alpha 2 glycoprotein promotes Th17 differentiation and collagen-induced arthritis in mice through enhancement of TGF- β -Smad2 signaling in naïve helper T cells. *Arthritis Research & Therapy*, 19(1). <https://doi.org/10.1186/s13075-017-1349-2>
- Wang, X., Abraham, S., McKenzie, J. A. G., Jeffs, N., Swire, M., Tripathi, V. B., Luhmann, U. F. O., Lange, C. A. K., Zhai, Z., Arthur, H. M., Bainbridge, J. W. B., Moss, S. E., & Greenwood, J. (2013). LRG1 promotes angiogenesis by modulating endothelial TGF- β signalling. *Nature*, 499(7458), 306–311. <https://doi.org/10.1038/nature12345>
- Wang, Y., Xu, J., Zhang, X., Wang, C., Huang, Y., Dai, K., & Zhang, X. (2017). TNF- α -induced LRG1 promotes angiogenesis and mesenchymal stem cell migration in the subchondral bone during osteoarthritis. *Cell Death & Disease*, 8(3), e2715–e2715. <https://doi.org/10.1038/cddis.2017.129>
- Wang, Z. V., & Scherer, P. E. (2016). Adiponectin, the past two decades. *Journal of Molecular Cell Biology*, 8(2), 93–100. <https://doi.org/10.1093/jmcb/mjw011>
- Weisberg, S. P., Hunter, D., Huber, R., Lemieux, J., Slaymaker, S., Vaddi, K., Charo, I., Leibel, R. L., & Jr.,

- A. W. F. (2006). CCR2 modulates inflammatory and metabolic effects of high-fat feeding. *Journal of Clinical Investigation*, 116(1), 115–124. <https://doi.org/10.1172/jci24335>
- Weisberg, S. P., McCann, D., Desai, M., Rosenbaum, M., Leibel, R. L., & Ferrante, A. W. (2003). Obesity is associated with macrophage accumulation in adipose tissue. *Journal of Clinical Investigation*, 112(12), 1796–1808. <https://doi.org/10.1172/jci19246>
- Wernstedt Asterholm, I., Tao, C., Morley, T. S., Wang, Q. A., Delgado-Lopez, F., Wang, Z. V., & Scherer, P. E. (2014). Adipocyte Inflammation Is Essential for Healthy Adipose Tissue Expansion and Remodeling. *Cell Metabolism*, 20(1), 103–118. <https://doi.org/10.1016/j.cmet.2014.05.005>
- World Health Organisation. (2018, February 16). *Obesity and overweight*. Who.Int; World Health Organization: WHO. <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>
- Wu, D., Molofsky, A. B., Liang, H.-E., Ricardo-Gonzalez, R. R., Jouihan, H. A., Bando, J. K., Chawla, A., & Locksley, R. M. (2011). Eosinophils Sustain Alternatively Activated Macrophages Associated with Glucose Homeostasis. *Science*, 332(6026), 243–247. <https://doi.org/10.1126/science.1201475>
- Xiao, S., & Zhu, H. (2018). Leucine-Rich Alpha-2-Glycoprotein1 Gene Interferes with Regulation of Apoptosis in Leukemia KASUMI-1 Cells. *Medical Science Monitor*, 24, 8348–8356. <https://doi.org/10.12659/msm.911249>
- Xie, Z.-B., Zhang, Y.-F., Jin, C., Mao, Y.-S., & Fu, D.-L. (2019). LRG-1 promotes pancreatic cancer growth and metastasis via modulation of the EGFR/p38 signaling. *Journal of Experimental & Clinical Cancer Research*, 38(1). <https://doi.org/10.1186/s13046-019-1088-0>
- Yang, F.-J., Hsieh, C.-Y., Shu, K.-H., Chen, I.-Y., Pan, S.-Y., Chuang, Y.-F., Chiu, Y.-L., & Yang, W.-S. (2020). Plasma Leucine-Rich α -2-Glycoprotein 1 Predicts Cardiovascular Disease Risk in End-Stage Renal Disease. *Scientific Reports*, 10(1). <https://doi.org/10.1038/s41598-020-62989-7>