

DAFTAR PUSTAKA

1. WHO. Noncommunicable Diseases. <https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases> (2021).
2. Roth, G. A. *et al.* Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* **392**, 1736–1788 (2018).
3. Thakur, J. S., Paika, R. & Singh, S. Burden of noncommunicable diseases and implementation challenges of National NCD Programmes in India. *Med. J. Armed Forces India* **76**, 261–267 (2020).
4. Ministry of Health of Republic Indonesia. NCD Prevention and Control in Indonesia 2016. (2016).
5. Ezzati, P. M. NCD Countdown 2030: pathways to achieving Sustainable Development Goal target 3.4. *Lancet* **396**, 918–934 (2020).
6. Purnamasari, D. The Emergence of Non-communicable Disease in Indonesia. *Acta Med. Indones.* **50**, 273–274 (2018).
7. Lear, S. A. *et al.* The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. *Lancet* **390**, 2643–2654 (2017).
8. Bull, F. C. *et al.* World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br. J. Sports Med.* **54**, 1451–1462 (2020).
9. Visseren, F. L. J. *et al.* 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur. Heart J.* **42**, 3227–3337 (2021).
10. Wahid, A. *et al.* Quantifying the Association Between Physical Activity and Cardiovascular Disease and Diabetes: A Systematic Review and Meta-Analysis. *J. Am. Heart Assoc.* **5**, (2016).
11. Peters, R. *et al.* Common risk factors for major noncommunicable disease, a systematic overview of reviews and commentary: the implied potential for targeted risk reduction. *Ther. Adv. Chronic Dis.* **10**, 1–14 (2019).

12. Tremblay, M. Letter to the editor: Standardized use of the terms ‘sedentary’ and ‘sedentary behaviours’. *Appl. Physiol. Nutr. Metab.* **37**, 540–542 (2012).
13. Tremblay, M. S. *et al.* Sedentary Behavior Research Network (SBRN) - Terminology Consensus Project process and outcome. *Int. J. Behav. Nutr. Phys. Act.* **14**, 1–17 (2017).
14. Park, J. H., Moon, J. H., Kim, H. J., Kong, M. H. & Oh, Y. H. Sedentary Lifestyle: Overview of Updated Evidence of Potential Health Risks. *Korean J. Fam. Med.* **41**, 365–373 (2020).
15. Jetté, M., Sidney, K. & Blümchen, G. Metabolic equivalents (METs) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin. Cardiol.* **13**, 555–565 (1990).
16. RI, P. PP REPUBLIK INDONESIA NOMOR 21 TAHUN 2020 TENTANG PEMBATASAN SOSIAL BERSKALA BESAR DALAM RANGKA PERCEPATAN PENANGANAN CORONA WRUS DISEASE 2019 (COVID-Ig) DENGAN. *Website* **2019**, 8 (2020).
17. Alricsson, M. & Kahlin, Y. Physical activity and health in adolescents. *Sedentary Lifestyle Predict. Factors, Heal. Risks Physiol. Implic.* **15**, 115–130 (2016).
18. Elagizi, A., Kachur, S., Carbone, S., Lavie, C. J. & Blair, S. N. A Review of Obesity, Physical Activity, and Cardiovascular Disease. *Curr. Obes. Rep.* **9**, 571–581 (2020).
19. Kodama, S. Cardiorespiratory Fitness as a Quantitative Predictor of All-Cause Mortality and Cardiovascular Events. *J. Am. Med. Assoc.* **301**, 2024–2035 (2009).
20. Imboden, M. T. *et al.* The Association between the Change in Directly Measured Cardiorespiratory Fitness across Time and Mortality Risk. *Prog. Cardiovasc. Dis.* **62**, 157–162 (2019).
21. ACSM. *ACSM’s Guidelines for Exercise Testing and Prescription.* (Wolters Kluwer, 2018).
22. Kaminsky, L. A. *et al.* Cardiorespiratory fitness and cardiovascular disease - The past, present, and future. *Prog. Cardiovasc. Dis.* **62**, 86–93 (2019).

23. Barry, V. W. *et al.* Fitness vs. fatness on all-cause mortality: A meta-analysis. *Prog. Cardiovasc. Dis.* **56**, 382–390 (2014).
24. Guo, Y., Chen, J. & Qiu, H. Novel Mechanisms of Exercise-Induced Cardioprotective Factors in Myocardial Infarction. *Front. Physiol.* **11**, 1–12 (2020).
25. Bei, Y. *et al.* Exercise-induced circulating extracellular vesicles protect against cardiac ischemia–reperfusion injury. *Basic Res. Cardiol.* **112**, (2017).
26. Xi, Y., Gong, D. W. & Tian, Z. FSTL1 as a Potential Mediator of Exercise-Induced Cardioprotection in Post-Myocardial Infarction Rats. *Sci. Rep.* **6**, 1–11 (2016).
27. Moghetti, P., Bacchi, E., Brangani, C., Donà, S. & Negri, C. Metabolic Effects of Exercise. *Front. Horm. Res.* **47**, 44–57 (2016).
28. Wang, R. *et al.* Impacts of exercise intervention on various diseases in rats. *J. Sport Heal. Sci.* **9**, 211–227 (2020).
29. Vujic, A. *et al.* Exercise induces new cardiomyocyte generation in the adult mammalian heart. *Nat. Commun.* **9**, 1–9 (2018).
30. Brett, J. O. *et al.* Exercise rejuvenates quiescent skeletal muscle stem cells in old mice through restoration of Cyclin D1. *Nat. Metab.* **2**, 307–317 (2020).
31. Quindry, J. & Hamilton, K. Exercise and Cardiac Preconditioning Against Ischemia Reperfusion Injury. *Curr. Cardiol. Rev.* **9**, 220–229 (2013).
32. Borges, J. P. & da Silva Verdoorn, K. Cardiac ischemia/reperfusion injury: The beneficial effects of exercise. *Adv. Exp. Med. Biol.* **999**, 155–179 (2017).
33. Radák, Z. *et al.* Exercise preconditioning against hydrogen peroxide-induced oxidative damage in proteins of rat myocardium. *Arch. Biochem. Biophys.* **376**, 248–251 (2000).
34. Koyama, K. Exercise-induced oxidative stress: A tool for “hormesis” and “adaptive response”. *J. Phys. Fit. Sport. Med.* **3**, 115–120 (2014).
35. Gunadi, J. W. *et al.* Cardiac hypertrophy is stimulated by altered training intensity and correlates with autophagy modulation in male Wistar rats. *BMC Sports Sci. Med. Rehabil.* **11**, 1–9 (2019).

36. Boström, P. *et al.* C/EBP β controls exercise-induced cardiac growth and protects against pathological cardiac remodeling. *Cell* **143**, 1072–1083 (2010).
37. Radak, Z., Zhao, Z., Koltai, E., Ohno, H. & Atalay, M. Oxygen consumption and usage during physical exercise: The balance between oxidative stress and ROS-dependent adaptive signaling. *Antioxidants Redox Signal.* **18**, 1208–1246 (2013).
38. Hitomi, Y. *et al.* Acute exercise increases expression of extracellular superoxide dismutase in skeletal muscle and the aorta. *Redox Rep.* **13**, 213–216 (2008).
39. Kawamura, T. & Muraoka, I. Exercise-induced oxidative stress and the effects of antioxidant intake from a physiological viewpoint. *Antioxidants* **7**, (2018).
40. Lennon, S. L. *et al.* Exercise and myocardial tolerance to ischaemia-reperfusion. *Acta Physiol. Scand.* **182**, 161–169 (2004).
41. Bowles, D. K. & Starnes, J. W. Exercise training improves metabolic response after ischemia in isolated working rat heart. *J. Appl. Physiol.* **76**, 1608–1614 (1994).
42. Peters, M. C. *et al.* Follistatin-like 1 promotes proliferation of matured human hypoxic iPSC-cardiomyocytes and is secreted by cardiac fibroblasts. *Mol. Ther. - Methods Clin. Dev.* **25**, 3–16 (2022).
43. Pinckard, K., Baskin, K. K. & Stanford, K. I. Effects of Exercise to Improve Cardiovascular Health. *Front. Cardiovasc. Med.* **6**, 1–12 (2019).
44. Szabó, M. R., Pipicz, M., Csont, T. & Csonka, C. Modulatory effect of myokines on reactive oxygen species in ischemia/reperfusion. *Int. J. Mol. Sci.* **21**, 1–26 (2020).
45. Scheele, C., Nielsen, S. & Pedersen, B. K. ROS and myokines promote muscle adaptation to exercise. *Trends Endocrinol. Metab.* **20**, 95–99 (2009).
46. M. Shibamura, J. Mashimo, A. Mita, T. Kuroki, A. & Nose, K. Cloning from a mouse osteoblastic cell line of a set of transforming-growth-factor-beta 1-regulated genes, one of which seems to encode a follistatin-related

- polypeptide. *Eur. J. Biochem.* **217**, 13–19 (1993).
47. Miyabe, M. *et al.* Muscle-derived follistatin-like 1 functions to reduce neointimal formation after vascular injury. *Cardiovasc. Res.* **103**, 111–120 (2014).
 48. Sanchis-Gomar, F., Perez-Quilis, C. & Lucia, A. Overexpressing FSTL1 for Heart Repair. *Trends Mol. Med.* **22**, 353–354 (2016).
 49. Horak, M., Kuruczova, D., Zlamal, F., Tomandl, J. & Bienertova-Vasku, J. Follistatin-like 1 is downregulated in morbidly and super obese central-European population. *Dis. Markers* **2018**, (2018).
 50. Xu, Xiaohui; Zhang, Tingran; Mokou, Mani; Li, Ling; li, Peng; Song, Jinlin; Liu, Hua; Zhu, Zhiming; Liu, Dongfang; Yang, Mengliu; Yang, G. FSTL1 as a novel adipo-myokine related to insulin resistance and Physical activity. *J. Clin. Endocrinol. Metab.* (2020) doi:10.1210/clinem/dgaa629.
 51. Kon, M., Tanimura, Y. & Yoshizato, H. Effects of acute endurance exercise on follistatin-like 1 and apelin in the circulation and metabolic organs in rats. *Arch. Physiol. Biochem.* **0**, 1–5 (2020).
 52. Kon, M., Ebi, Y. & Nakagaki, K. Effects of acute sprint interval exercise on follistatin-like 1 and apelin secretions. *Arch. Physiol. Biochem.* **127**, 223–227 (2021).
 53. Hayakawa, S. *et al.* Association of circulating follistatin-like 1 levels with inflammatory and oxidative stress markers in healthy men. *PLoS One* **11**, 1–8 (2016).
 54. Hu, S., Liu, H., Hu, Z., Li, L. & Yang, Y. Follistatin-like 1: A dual regulator that promotes cardiomyocyte proliferation and fibrosis. *J. Cell. Physiol.* **235**, 5893–5902 (2020).
 55. Mattiotti, A., Prakash, S., Barnett, P. & van den Hoff, M. J. B. Follistatin-like 1 in development and human diseases. *Cell. Mol. Life Sci.* **75**, 2339–2354 (2018).
 56. Shimano, M. *et al.* Cardiac myocyte follistatin-like 1 functions to attenuate hypertrophy following pressure overload. *Proc. Natl. Acad. Sci. U. S. A.* **108**, 899–906 (2011).

57. Ouchi, N. *et al.* Follistatin-like 1, a secreted muscle protein, promotes endothelial cell function and revascularization in ischemic tissue through a nitric-oxide synthase-dependent mechanism. *J. Biol. Chem.* **283**, 32802–32811 (2008).
58. Xi, Y., Hao, M. & Tian, Z. Resistance Exercise Increases the Regulation of Skeletal Muscle FSTL1 Consequently Improving Cardiac Angiogenesis in Rats with Myocardial Infarctions. *J. Sci. Sport Exerc.* **1**, 78–87 (2019).
59. Shen, H. *et al.* Follistatin-like 1 protects mesenchymal stem cells from hypoxic damage and enhances their therapeutic efficacy in a mouse myocardial infarction model. *Stem Cell Res. Ther.* **10**, 1–14 (2019).
60. Cheng, K.-Y. *et al.* Follistatin-like protein 1 suppressed pro-inflammatory cytokines expression during neuroinflammation induced by lipopolysaccharide. *J. Mol. Histol.* **48**, 63–72 (2017).
61. Varga, I., Kyselovič, J., Galfiova, P. & Danisovic, L. The non-cardiomyocyte cells of the heart. their possible roles in exercise-induced cardiac regeneration and remodeling. *Adv. Exp. Med. Biol.* **999**, 117–136 (2017).
62. Wei, K. *et al.* Epicardial FSTL1 reconstitution regenerates the adult mammalian heart. *Nature* **525**, 479–485 (2015).
63. Ogura, Y. *et al.* Therapeutic impact of follistatin-like 1 on myocardial ischemic injury in preclinical models. *Circulation* **126**, 1728–1738 (2012).
64. Seki, M. *et al.* Acute and chronic increases of circulating FSTL1 normalize energy substrate metabolism in pacing-induced heart failure. *Circ. Hear. Fail.* **11**, 1–12 (2018).
65. Xi, Y. *et al.* Dynamic resistance exercise increases skeletal muscle-derived FSTL1 inducing cardiac angiogenesis via DIP2A–Smad2/3 in rats following myocardial infarction. *J. Sport Heal. Sci.* **10**, 594–603 (2021).
66. Schroeder, E. C., Franke, W. D., Sharp, R. L. & Lee, D. chul. Comparative effectiveness of aerobic, resistance, and combined training on cardiovascular disease risk factors: A randomized controlled trial. *PLoS One* **14**, 1–14 (2019).

67. Mohamed, T. M. A. *et al.* Regulation of Cell Cycle to Stimulate Adult Cardiomyocyte Proliferation and Cardiac Regeneration. *Cell* **173**, 104-116.e12 (2018).
68. Shaw, R. J. LKB1 and AMP-activated protein kinase control of mTOR signalling and growth. *Acta Physiol.* **196**, 65–80 (2009).
69. Marino, F. *et al.* Role of c-kit in myocardial regeneration and aging. *Front. Endocrinol. (Lausanne)*. **10**, 1–15 (2019).
70. Averous, J., Fonseca, B. D. & Proud, C. G. Regulation of cyclin D1 expression by mTORC1 signaling requires eukaryotic initiation factor 4E-binding protein 1. *Oncogene* **27**, 1106–1113 (2008).
71. Tamamori-Adachi, M. *et al.* Critical role of cyclin D1 nuclear import in cardiomyocyte proliferation. *Circ. Res.* **92**, 1–5 (2003).
72. Muisse-Helmericks, R. C. *et al.* Cyclin D expression is controlled post-transcriptionally via a phosphatidylinositol 3-kinase/Akt-dependent pathway. *J. Biol. Chem.* **273**, 29864–29872 (1998).
73. Xiao, J. *Physical Exercise for Human Health. Advances in Experimental Medicine and Biology* vol. 1228 (Springer International Publishing, 2020).
74. Bollyky, T. J., Templin, T., Andridge, C. & Dieleman, J. L. Understanding the relationships between noncommunicable diseases, unhealthy lifestyles, and country wealth. *Health Aff.* **34**, 1464–1471 (2015).
75. Andriyani, F. D., Biddle, S. J. H., Arovah, N. I. & de Cocker, K. Physical activity and sedentary behavior research in Indonesian youth: A scoping review. *Int. J. Environ. Res. Public Health* **17**, 1–15 (2020).
76. Aparicio, H. J. *et al.* *Heart Disease and Stroke Statistics-2021 Update A Report from the American Heart Association. Circulation* (2021). doi:10.1161/CIR.0000000000000950.
77. Park, J. H. *et al.* Association between sedentary time and cardiovascular risk factors in Korean adults. *Korean J. Fam. Med.* **39**, 29–36 (2018).
78. Seth, A. Exercise prescription: What does it mean for primary care? *Br. J. Gen. Pract.* **64**, 12–13 (2014).
79. Rees-Punia, E. *et al.* Mortality Risk Reductions for Replacing Sedentary

- Time With Physical Activities. *Am. J. Prev. Med.* **56**, 736–741 (2019).
80. Radak, Z., Chung, H. Y., Koltai, E., Taylor, A. W. & Goto, S. Exercise, oxidative stress and hormesis. *Ageing Res. Rev.* **7**, 34–42 (2008).
 81. Burnet, K., Kelsch, E., Zieff, G., Moore, J. B. & Stoner, L. How fitting is F.I.T.T.?: A perspective on a transition from the sole use of frequency, intensity, time, and type in exercise prescription. *Physiol. Behav.* **199**, 33–34 (2019).
 82. Papageorgiou, C. D. *et al.* Hormesis-Like Benefits of Physical Exercises Due To Increased Reactive Oxygen Species. *Phys. Educ. Sport. Kinesither. Res. J. /PESKRJ* **1**, 76–84 (2016).
 83. Garber, C. E. *et al.* Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. *Med. Sci. Sports Exerc.* **43**, 1334–1359 (2011).
 84. Fox, S. M. & Haskell, W. L. Physical activity and the prevention of coronary heart disease. *Bull. N. Y. Acad. Med.* **44**, 950–67 (1968).
 85. Uth, N., Sørensen, H., Overgaard, K. & Pedersen, P. K. Estimation of VO₂max from the ratio between HR_{max} and HR_{rest} - The heart rate ratio method. *Eur. J. Appl. Physiol.* **91**, 111–115 (2004).
 86. Bouviere, J. *et al.* Exercise-stimulated ros sensitive signaling pathways in skeletal muscle. *Antioxidants* **10**, 1–21 (2021).
 87. Loprinzi, P. D., Maskalick, S. & Veigl, V. L. *Exercise Physiology. Orthopaedic Physical Therapy Secrets: Third Edition* (Elsevier Inc., 2017). doi:10.1016/B978-0-323-28683-1.00005-9.
 88. Yu, M., Corletto, J. & Barkley, L. C. Exercise Prescription. *Curr. Sports Med. Rep.* **20**, 627–628 (2021).
 89. WILLIAMS, P. T. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. *Med. Sci. Sports Exerc.* 754–761 (2001) doi:10.1097/00005768-200105000-00012.
 90. Goncalves, R. L. S., Quinlan, C. L., Perevoshchikova, I. V., Hey-Mogensen, M. & Brand, M. D. Sites of Superoxide and Hydrogen Peroxide Production

- by Muscle Mitochondria Assessed ex Vivo under Conditions Mimicking Rest and Exercise. *J. Biol. Chem.* **290**, 209–227 (2015).
91. Starnes, J. W., Taylor, R. P. & Ciccolo, J. T. Habitual low-intensity exercise does not protect against myocardial dysfunction after ischemia in rats. *Eur. J. Cardiovasc. Prev. Rehabil.* **12**, 169–174 (2005).
 92. LIBONATI, J. R. *et al.* Reduced ischemia and reperfusion injury following exercise training. *Med. & Sci. Sport. & Exerc.* **29**, 509–516 (1997).
 93. Faltová, E., Mráz, M., Parížková, J. & Sedivý, J. Physical activity of different intensities and the development of myocardial resistance to injury. *Physiol. Bohemoslov.* **34**, 289–96 (1985).
 94. Romijn, J. A. *et al.* Regulation of endogenous fat and carbohydrate metabolism in relation to exercise intensity and duration. *Am. J. Physiol. - Endocrinol. Metab.* **265**, 380–391 (1993).
 95. Masoud, G. N. & Li, W. HIF-1 α pathway: Role, regulation and intervention for cancer therapy. *Acta Pharm. Sin. B* **5**, 378–389 (2015).
 96. Rasbach, K. A. *et al.* PGC-1 α regulates a HIF2 α -dependent switch in skeletal muscle fiber types. *Proc. Natl. Acad. Sci. U. S. A.* **107**, 21866–21871 (2010).
 97. Liang, H. & Ward, W. F. PGC-1 α : A key regulator of energy metabolism. *Am. J. Physiol. - Adv. Physiol. Educ.* **30**, 145–151 (2006).
 98. Sylviana, N., Goenawan, H., Susanti, Y., Lesmana, R. & Megantara, I. Effect of different intensities aerobic exercise to cardiac angiogenesis regulation on Wistar rats. *Pol. J. Vet. Sci.* **25**, 119–128 (2022).
 99. Griendling, K. K. & FitzGerald, G. A. Oxidative Stress and Cardiovascular Injury Part I: Basic Mechanisms and In Vivo Monitoring of ROS. *Circulation* **108**, 1912–1916 (2003).
 100. Buetler, T. M., Krauskopf, A. & Ruedg, U. T. Role of superoxide as a signaling molecule. *News Physiol. Sci.* **19**, 120–123 (2004).
 101. Louzada, R. A. *et al.* Redox Signaling in Widespread Health Benefits of Exercise. *Antioxidants Redox Signal.* **33**, 745–760 (2020).
 102. Sakellariou, G. K. *et al.* Studies of Mitochondrial and Nonmitochondrial Sources Implicate Nicotinamide Adenine Dinucleotide Phosphate

- Oxidase(s) in the Increased Skeletal Muscle Superoxide Generation That Occurs During Contractile Activity. *Antioxid. Redox Signal.* **18**, 603–621 (2013).
103. Michaelson, L. P., Shi, G., Ward, C. W. & Rodney, G. G. Mitochondrial redox potential during contraction in single intact muscle fibers. *Muscle Nerve* **42**, 522–529 (2010).
 104. Wong, H.-S., Dighe, P. A., Mezera, V., Monternier, P.-A. & Brand, M. D. Production of superoxide and hydrogen peroxide from specific mitochondrial sites under different bioenergetic conditions. *J. Biol. Chem.* **292**, 16804–16809 (2017).
 105. Fukai, T. *et al.* Regulation of the vascular extracellular superoxide dismutase by nitric oxide and exercise training. *J. Clin. Invest.* **105**, 1631–1639 (2000).
 106. Sylviana, N., Gunawan, H., Lesmana, R., Purba, A. & Akbar, I. B. The Effect of Astaxanthin and Regular Training on Dynamic Pattern of Oxidative Stress on Male under Strenuous Exercise. *Indones. J. Clin. Pharm.* **6**, 46–54 (2017).
 107. CHACAROUN, S. *et al.* Hypoxic Exercise Training to Improve Exercise Capacity in Obese Individuals. *Med. Sci. Sport. Exerc.* **52**, 1641–1649 (2020).
 108. Moonen, L., D’Haese, P. C. & Vervaet, B. A. Epithelial cell cycle behaviour in the injured kidney. *Int. J. Mol. Sci.* **19**, (2018).
 109. Verbon, E. H., Post, J. A. & Boonstra, J. The influence of reactive oxygen species on cell cycle progression in mammalian cells. *Gene* **511**, 1–6 (2012).
 110. Boonstra, J. & Post, J. A. Molecular events associated with reactive oxygen species and cell cycle progression in mammalian cells. *Gene* **337**, 1–13 (2004).
 111. Kim, J., Seok, Y. M., Jung, K.-J. & Park, K. M. Reactive oxygen species/oxidative stress contributes to progression of kidney fibrosis following transient ischemic injury in mice. *Am. J. Physiol. Physiol.* **297**, F461–F470 (2009).
 112. LEON, A. S. & SANCHEZ, O. A. Response of blood lipids to exercise training alone or combined with dietary intervention. *Med. Sci. Sports Exerc.*

- 33**, S502–S515 (2001).
113. Ploug, T., Galbo, H. & Richter, E. A. Increased muscle glucose uptake during contractions: no need for insulin. *Am. J. Physiol. Metab.* **247**, E726–E731 (1984).
 114. Yang, S. *et al.* Association between circulating follistatin-like-1 and metabolic syndrome in middle-aged and old population: A cross-sectional study. *Diabetes. Metab. Res. Rev.* **37**, (2021).
 115. Ciumărnean, L. *et al.* Cardiovascular risk factors and physical activity for the prevention of cardiovascular diseases in the elderly. *Int. J. Environ. Res. Public Health* **19**, (2022).
 116. Powers, S. K., Smuder, A. J., Kavazis, A. N. & Quindry, J. C. Mechanisms of exercise-induced cardioprotection. *Physiology* **29**, 27–38 (2014).
 117. Anderson, L. *et al.* Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease Cochrane Systematic Review and Meta-Analysis. *J. Am. Coll. Cardiol.* **67**, 1–12 (2016).
 118. Frasier, C. R., Moore, R. L. & Brown, D. A. Exercise-induced cardiac preconditioning: How exercise protects your achy-breaky heart. *J. Appl. Physiol.* **111**, 905–915 (2011).
 119. Geng, Y. *et al.* Follistatin-like 1 (Fstl1) is a bone morphogenetic protein (BMP) 4 signaling antagonist in controlling mouse lung development. *Proc. Natl. Acad. Sci. U. S. A.* **108**, 7058–7063 (2011).
 120. Ouchi, N. *et al.* DIP2A functions as a FSTL1 receptor. *J. Biol. Chem.* **285**, 7127–7134 (2010).
 121. Li, W. *et al.* Molecular functions of FSTL1 in the osteoarthritis. *Int. Immunopharmacol.* **83**, 106465 (2020).
 122. Parfenova, O. K., Kukes, V. G. & Grishin, D. V. Follistatin-like proteins: Structure, functions and biomedical importance. *Biomedicines* **9**, 1–16 (2021).
 123. Li, W. *et al.* Molecular functions of FSTL1 in the osteoarthritis. *Int. Immunopharmacol.* **83**, 106465 (2020).
 124. Xiaohui Xu, Tingran Zhang, Mani Mokou, Ling Li, Peng Li, Jinlin Song,

- Hua Liu, Zhiming Zhu, Dongfang Liu, Mengliu Yang, G. Y. Follistatin-like 1 as a Novel Adipomyokine Related to Insulin Resistance and Physical Activity. *J. Clin. Endocrinol. Metab.* **105**, e4499–e4509 (2020).
125. Maruyama, S. *et al.* Follistatin-like 1 promotes cardiac fibroblast activation and protects the heart from rupture. *EMBO Mol. Med.* **8**, 949–966 (2016).
 126. Zhang, G. L., Sun, M. L. & Zhang, X. A. Exercise-Induced Adult Cardiomyocyte Proliferation in Mammals. *Frontiers in Physiology* vol. 12 1–8 (2021).
 127. Oshima, Y. *et al.* Follistatin-like 1 is an Akt-regulated cardioprotective factor that is secreted by the heart. *Circulation* **117**, 3099–3108 (2008).
 128. Yang, W., Duan, Q., Zhu, X., Tao, K. & Dong, A. Follistatin-Like 1 Attenuates Ischemia/Reperfusion Injury in Cardiomyocytes via Regulation of Autophagy. *Biomed Res. Int.* **2019**, (2019).
 129. Hayakawa, S. *et al.* Cardiac Myocyte-Derived Follistatin-Like 1 Prevents Renal Injury in a Subtotal Nephrectomy Model. *J. Am. Soc. Nephrol.* **26**, 636–646 (2015).
 130. Le Ludec, J. B. *et al.* An Immunomodulatory Role for Follistatin-Like 1 in Heart Allograft Transplantation. *Am. J. Transplant.* **8**, 2297–2306 (2008).
 131. Li, D. *et al.* Follistatin-like protein 1 is elevated in systemic autoimmune diseases and correlated with disease activity in patients with rheumatoid arthritis. *Arthritis Res. Ther.* **13**, R17 (2011).
 132. Miyamae, T. *et al.* Follistatin-Like Protein-1 Is a Novel Proinflammatory Molecule. *J. Immunol.* **177**, 4758–4762 (2006).
 133. Clutter, S. D., Wilson, D. C., Marinov, A. D. & Hirsch, R. Follistatin-Like Protein 1 Promotes Arthritis by Up-Regulating IFN- γ . *J. Immunol.* **182**, 234–239 (2009).
 134. Fan, N. *et al.* Follistatin-like 1: A potential mediator of inflammation in obesity. *Mediators Inflamm.* **2013**, (2013).
 135. Sylva, M., Moorman, A. F. M. & Van den Hoff, M. J. B. Follistatin-like 1 in vertebrate development. *Birth Defects Res. Part C - Embryo Today Rev.* **99**, 61–69 (2013).

136. Reddy, S. P. *et al.* Novel Glioblastoma Markers with Diagnostic and Prognostic Value Identified through Transcriptome Analysis. *Clin. Cancer Res.* **14**, 2978–2987 (2008).
137. Liu, Y. *et al.* Follistatin-like protein 1 promotes inflammatory reactions in nucleus pulposus cells by interacting with the MAPK and NF κ B signaling pathways. *Oncotarget* **8**, 43023–43034 (2017).
138. Murakami, K. *et al.* Follistatin-related protein/follistatin-like 1 evokes an innate immune response via CD14 and toll-like receptor 4. *FEBS Lett.* **586**, 319–324 (2012).
139. Mukhopadhyay, M. *et al.* Cloning, genomic organization and expression pattern of a novel *Drosophila* gene, the disco-interacting protein 2 (dip2), and its murine homolog. *Gene* **293**, 59–65 (2002).
140. Zhang, L. *et al.* Expression Patterns and Potential Biological Roles of Dip2a. *PLoS One* **10**, 1–16 (2015).
141. Zhang, L. Q. *et al.* Functional prediction and characterization of Dip2 gene in mice. *PLoS One* **10**, 421–428 (2019).
142. Winnepeninckx, B. *et al.* CGG-Repeat Expansion in the DIP2B Gene Is Associated with the Fragile Site FRA12A on Chromosome 12q13.1. *Am. J. Hum. Genet.* **80**, 221–231 (2007).
143. Adlat, S. *et al.* Global transcriptome study of Dip2B-deficient mouse embryonic lung fibroblast reveals its important roles in cell proliferation and development. *Comput. Struct. Biotechnol. J.* **18**, 2381–2390 (2020).
144. Tanaka, M. *et al.* DIP2 disco-interacting protein 2 homolog A (*Drosophila*) is a candidate receptor for follistatin-related protein/follistatin-like 1 - Analysis of their binding with TGF- β superfamily proteins. *FEBS J.* **277**, 4278–4289 (2010).
145. Kudo-Saito, C. *et al.* Blocking the FSTL1-DIP2A Axis Improves Anti-tumor Immunity. *Cell Rep.* **24**, 1790–1801 (2018).
146. Karar, J. & Maity, A. PI3K/AKT/mTOR Pathway in Angiogenesis. *Front. Mol. Neurosci.* **4**, 1–8 (2011).
147. Wang, M., Zhang, J. & Gong, N. Role of the PI3K/Akt signaling pathway in

- liver ischemia reperfusion injury: a narrative review. *Ann. Palliat. Med.* **11**, 806–817 (2022).
148. Abeyrathna, P. & Su, Y. The critical role of Akt in cardiovascular function. *Vascul. Pharmacol.* **74**, 38–48 (2015).
 149. Zhao, E. Y., Efendizade, A., Cai, L. & Ding, Y. The role of Akt (protein kinase B) and protein kinase C in ischemia–reperfusion injury. *Neurol. Res.* **38**, 301–308 (2016).
 150. Easton, R. M. *et al.* Role for Akt3/Protein Kinase B γ in Attainment of Normal Brain Size. *Mol. Cell. Biol.* **25**, 1869–1878 (2005).
 151. Phung, T. L. *et al.* Akt1 and Akt3 Exert Opposing Roles in the Regulation of Vascular Tumor Growth. *Cancer Res.* **75**, 40–50 (2015).
 152. Qin, X., Jiang, B. & Zhang, Y. 4E-BP1, a multifactor regulated multifunctional protein. *Cell Cycle* **15**, 781–786 (2016).
 153. Wullschleger, S., Loewith, R. & Hall, M. N. TOR signaling in growth and metabolism. *Cell* **124**, 471–484 (2006).
 154. Blenis, J. TOR, the Gateway to Cellular Metabolism, Cell Growth, and Disease. *Cell* **171**, 10–13 (2017).
 155. Gonzalez, S. & Rallis, C. The TOR Signaling Pathway in Spatial and Temporal Control of Cell Size and Growth. *Front. Cell Dev. Biol.* **5**, (2017).
 156. Tian, Z., Hao, M. & Xi, Y. Resistance training activates the signaling pathway of FSTL1-Akt-mTOR and induces cardiomyocyte proliferation in rats with myocardial infarction. *China Sport Sci.* **38**, 40–47 (2018).
 157. Apró, W., Wang, L., Pontén, M., Blomstrand, E. & Sahlin, K. Resistance exercise induced mTORC1 signaling is not impaired by subsequent endurance exercise in human skeletal muscle. *Am. J. Physiol. - Endocrinol. Metab.* **305**, 22–32 (2013).
 158. Dieterle, A. M. *et al.* PDK1 controls upstream PI3K expression and PIP 3 generation. *Oncogene* **33**, 3043–3053 (2014).
 159. Yang, H. *et al.* Mechanisms of mTORC1 activation by RHEB and inhibition by PRAS40. *Nature* **552**, 368–373 (2017).
 160. Alberts, B. *et al.* *Molecular Biology of the Cell - An Overview of the Cell*

Cycle. (Garland Science, 2002).

161. Hartwell, L. H. & Weinert, T. A. Checkpoints: Controls that ensure the order of cell cycle events. *Science* (80-.). **246**, 629–634 (1989).
162. Jingwen, B., Yaochen, L. & Guojun, Z. Cell cycle regulation and anticancer drug discovery. *Cancer Biol. Med.* **14**, 348 (2017).
163. Li, V. C. & Kirschner, M. W. Molecular ties between the cell cycle and differentiation in embryonic stem cells. *Proc. Natl. Acad. Sci. U. S. A.* **111**, 9503–9508 (2014).
164. Canaud, G. & Bonventre, J. V. Cell cycle arrest and the evolution of chronic kidney disease from acute kidney injury. *Nephrol. Dial. Transplant.* **30**, 575–583 (2015).
165. Walsh, S., Pontén, A., Fleischmann, B. K. & Jovinge, S. Cardiomyocyte cell cycle control and growth estimation in vivo-An analysis based on cardiomyocyte nuclei. *Cardiovasc. Res.* **86**, 365–373 (2010).
166. Iyer, D. & Rhind, N. The Intra-S Checkpoint Responses to DNA Damage. *Genes (Basel)*. **8**, 74 (2017).
167. Lazzaro, F. *et al.* RNase H and Postreplication Repair Protect Cells from Ribonucleotides Incorporated in DNA. *Mol. Cell* **45**, 99–110 (2012).
168. Ding, L. *et al.* The roles of cyclin-dependent kinases in cell-cycle progression and therapeutic strategies in human breast cancer. *Int. J. Mol. Sci.* **21**, 1–28 (2020).
169. Karlsson-Rosenthal, C. & Millar, J. B. A. Cdc25: mechanisms of checkpoint inhibition and recovery. *Trends Cell Biol.* **16**, 285–292 (2006).
170. Vousden, K. H. & Lane, D. P. p53 in health and disease. *Nat. Rev. Mol. Cell Biol.* **8**, 275–283 (2007).
171. Ahn, J., Urist, M. & Prives, C. The Chk2 protein kinase. *DNA Repair (Amst)*. **3**, 1039–1047 (2004).
172. Jares, P., Donaldson, A. & Blow, J. J. The Cdc7/Dbf4 protein kinase: target of the S phase checkpoint? *EMBO Rep.* **1**, 319–322 (2000).
173. Wang, R. *et al.* Regulation of Cdc25C by ERK-MAP Kinases during the G2/M Transition. *Cell* **128**, 1119–1132 (2007).

174. Astuti, P. *et al.* MAPK Pathway Activation Delays G2/M Progression by Destabilizing Cdc25B. *J. Biol. Chem.* **284**, 33781–33788 (2009).
175. Détaïn, A., Redecker, D., Leborgne-Castel, N. & Ochatt, S. Structural conservation of WEE1 and its role in cell cycle regulation in plants. *Sci. Rep.* **11**, 23862 (2021).
176. Wook Chung, Y. *et al.* H₂O₂-induced AP-1 activation and its effect on p21WAF1/CIP1-mediated G2/M arrest in a p53-deficient human lung cancer cell. *Biochem. Biophys. Res. Commun.* **293**, 1248–1253 (2002).
177. Musacchio, A. Spindle assembly checkpoint: the third decade. *Philos. Trans. R. Soc. B Biol. Sci.* **366**, 3595–3604 (2011).
178. Lara-Gonzalez, P., Westhorpe, F. G. & Taylor, S. S. The Spindle Assembly Checkpoint. *Curr. Biol.* **22**, R966–R980 (2012).
179. Banerjee, I., Fuseler, J. W., Price, R. L., Borg, T. K. & Baudino, T. A. Determination of cell types and numbers during cardiac development in the neonatal and adult rat and mouse. *Am. J. Physiol. - Hear. Circ. Physiol.* **293**, 1883–1891 (2007).
180. Zhou, P. & Pu, W. T. Recounting cardiac cellular composition. *Circ. Res.* **118**, 368–370 (2016).
181. Zebrowski, D. C., Becker, R. & Engel, F. B. Towards regenerating the mammalian heart: Challenges in evaluating experimentally induced adult mammalian cardiomyocyte proliferation. *Am. J. Physiol. - Hear. Circ. Physiol.* **310**, H1045–H1054 (2016).
182. Rubart, M. & Field, L. J. Cardiac regeneration: Repopulating the heart. *Annu. Rev. Physiol.* **68**, 29–49 (2006).
183. Ahuja, P., Sdek, P. & MacLellan, W. R. Cardiac myocyte cell cycle control in development, disease, and regeneration. *Physiol. Rev.* **87**, 521–544 (2007).
184. Johnson, D. G. Role of E2F in cell cycle control and cancer. *Front. Biosci.* **3**, A291 (1998).
185. Tarawan, V. M. *et al.* Alteration of autophagy gene expression by different intensity of exercise in gastrocnemius and soleus muscles of wistar rats. *J. Sport. Sci. Med.* **18**, 146–154 (2019).

186. Yan, Z., Zeng, N., Li, J., Liao, T. & Ni, G. Cardiac Effects of Treadmill Running at Different Intensities in a Rat Model. *Front. Physiol.* **12**, 1–11 (2021).
187. Liu, W. *et al.* Physical exercise promotes proliferation and differentiation of endogenous neural stem cells via ERK in rats with cerebral infarction. *Mol. Med. Rep.* **18**, 1455–1464 (2018).
188. Lesmana, R. *et al.* The change in thyroid hormone signaling by altered training intensity in male rat skeletal muscle. *Endocr. J.* **63**, 727–738 (2016).
189. Roger, M. *The Design of Experiments: Statistical principles for practical application.* (Cambridge University Press, 1990).
190. Council, N. R. *Guide for the Care and Use of Laboratory Animals.* vol. 21 (National Academies Press, 2011).
191. Badan Pusat Statistik Kabupaten Sumedang. *Kecamatan Jatinangor dalam Angka 2021.* (2021).
192. Soya, H. *et al.* Threshold-like pattern of neuronal activation in the hypothalamus during treadmill running: Establishment of a minimum running stress (MRS) rat model. *Neurosci. Res.* **58**, 341–348 (2007).
193. Jones, J. H. Resource Book for the Design of Animal Exercise Protocols. *Am. J. Vet. Res.* **68**, 583–583 (2007).
194. Michinaga, S., Ishida, A., Takeuchi, R. & Koyama, Y. Endothelin-1 stimulates cyclin D1 expression in rat cultured astrocytes via activation of Sp1. *Neurochem. Int.* **63**, 25–34 (2013).
195. Nazari, Z., Nabiuni, M., Saeidi, M. & Golalipour, M. J. Gestational diabetes leads to down-regulation of CDK4-pRB-E2F1 pathway genes in pancreatic islets of rat offspring. *Iran. J. Basic Med. Sci.* **20**, 150–154 (2017).
196. Care, C. C. on A. Three Rs - Replacement, Reduction, Refinement. <https://ccac.ca/en/three-rs-and-ethics/the-three-rs.html> (2022).
197. Society, A. H. The Five Freedoms for Animals. 1 <https://www.animalhumanesociety.org/health/five-freedoms-animals?msclkid=944334bcb2b711eca302fbd51719abc3> (2022).
198. Swift, D. L. *et al.* The Effects of Exercise and Physical Activity on Weight

- Loss and Maintenance. *Prog. Cardiovasc. Dis.* **61**, 206–213 (2018).
199. Maksimowski, N. A. *et al.* Follistatin-like-1 (Fstl1) is a fibroblast-derived growth factor that contributes to progression of chronic kidney disease. *Int. J. Mol. Sci.* **22**, (2021).
 200. Zhang, Y. *et al.* Deficiency of follistatin-like protein 1 accelerates the growth of breascancer cells at lung metastatic sites. *J. Breast Cancer* **21**, 267–276 (2018).
 201. Bevivino, G. *et al.* Follistatin-like protein 1 sustains colon cancer cell growth and survival. *Oncotarget* **9**, 31278–31290 (2018).
 202. Qie, S. & Diehl, J. A. Cyclin D1, cancer progression, and opportunities in cancer treatment. *J. Mol. Med.* **94**, 1313–1326 (2016).
 203. Fassl, A., Geng, Y. & Sicinski, P. CDK4 and CDK6 kinases: From basic science to cancer therapy. *Science (80-.)*. **375**, (2022).
 204. Alao, J. P. The regulation of cyclin D1 degradation: Roles in cancer development and the potential for therapeutic invention. *Mol. Cancer* **6**, 1–16 (2007).
 205. Tamamori-Adachi, M. *et al.* Expression of cyclin D1 and CDK4 causes hypertrophic growth of cardiomyocytes in culture: A possible implication for cardiac hypertrophy. *Biochem. Biophys. Res. Commun.* **296**, 274–280 (2002).