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Irisin的生理效应及其研究进展

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摘　要

Irisin (鸢尾素)从最初被发现在脂肪细胞棕化过程中的作用后就一直被研究者们广泛关注。它在多种组织中均有表达，在运动后及二型糖尿病，孕期糖尿病患者中表达量发生变化。由于Irisin可以改善胰岛素抵抗，促进脂肪细胞棕化，故其在糖尿病及肥胖症治疗中具有应用潜力。Irisin在神经系统发育中具有重要作用，其含量与认知水平密切相关。本文就Irisin的发现及生理效应的研究展开综述。

关键词

Irisin，脂肪代谢，白色脂肪组织，棕色脂肪组织，二型糖尿病，FNDC5

Physiological Effects of Irisin and its Research Progress

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Abstract

Irisin has inspired great interests from scientists since it was discovered to be important for white fat browning. It is expressed in many different tissues and Irisin level has been shown to change

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after exercise and in Type 2 diabetes patients and gestational diabetes patients. Since Irisin improves insulin resistance and promotes fat browning, it has great potential in diabetes and obesity treatment. Irisin plays important role in nervous system development, and its level is closely related to cognitive level. This review summarizes the physiological effects of Irisin and its research progress.

Keywords

Irisin, Fat Metabolism, White Adipose Tissue, Brown Adipose Tissue, Type 2 Diabetes, FNDC5

1. Irisin 的发现

Irisin 是一种可以促进白色脂肪棕化的激素。Irisin 最初是在对 PGC1α 转基因小鼠的研究中发现的[1]。骨骼肌中表达量升高的 PGC1a 转基因小鼠不易患糖尿病或老年性肥胖，暗示这些小鼠的能量代谢系统具有特殊的改变。研究者们发现骨骼肌中的转基因 PGC1a 可诱导皮下脂肪的棕化。经过分析 PGC1a 转基因小鼠的基因表达谱发现，Fndc5 的表达量明显增加，而 Fndc5 处理确实可以诱导体外培养的脂肪细胞中棕色脂肪基因的表达。Fndc5 含有一个信号肽，两个纤维连接蛋白结构域和一个疏水结构域构成。质谱分析发现 Fndc5 在 112 位谷氨酸处被酶切后产生一种在小鼠和人之间一致性为 100%的多肽，由于这个多肽从骨骼肌到脂肪等其他组织的信使作用，依据希腊神话中的信使女神 Iris 而被命名为 Irisin。这一命名很好的概括了 Irisin 在运动后肌肉向脂肪(棕化和产热)以及其他和代谢相关组织传递中的化学信使作用。在表达 PGC1a 的骨骼肌细胞培养液中加入 Irisin 抗体后，其对于脂肪细胞中棕色脂肪基因表达的促进作用显著降低，暗示 Irisin 在脂肪细胞棕化中的重要作用。该研究还发现，Irisin 可以在高脂饮食小鼠体内高效地使白色脂肪组织发生棕化，增加能量消耗并提高葡萄糖耐受性。

2. Irisin 表达的组织

最初研究者们利用 Western [1]和 ELISA [2]的方法测定了血浆中 Irisin 的含量，并利用免疫反应确定了 *Irisin* 在心肌和骨骼肌中的表达[3]。随后越来越多的研究发现 *Irisin* 也在肝[4]，脾脏，肾脏，胰腺，皮肤，脂肪[5] [6]，汗腺，唾液腺，睾丸[7]，附睾，脑等组织中广泛地表达。这说明 Irisin 在细胞生理中起着重要的作用，而 Irisin 在多种组织器官中的其他功能则需要更多的研究来确认。

3. Irisin 在脂肪代谢中的作用

脂肪组织根据其颜色，解剖学位置，以及生物学功能的不同分为：白色脂肪组织(White Adipose Tissue, WAT)和棕色脂肪组织(Brown Adipose Tissue, BAT)。白色脂肪组织呈白色，主要在皮下以单细胞或在腹腔膜以紧密组织存在，其生物学功能为储存过多的能量。白色脂肪组织中油滴单个存在于每个细胞中，线粒体含量较少。棕色脂肪组织呈棕色，啮齿类动物中，棕色脂肪库主要存在于肩胛骨和胸部纵隔处[8]，其主要生物学功能为产热。棕色脂肪中油滴以多个小泡存在，线粒体数目很多。其线粒体膜上有 UCP1 (uncoupling protein 1)蛋白，可以将质子从线粒体质中泵到线粒体膜间隙[9]，此过程可产热，在新生儿调节体温过程中具有重要作用。两种脂肪细胞虽都从中胚层发育而来，但起源于不同的间叶细胞干细胞谱系。

棕色脂肪按其来源以及位置的不同分为两种：经典棕色脂肪或组成型棕色脂肪(classicalBAT, cBAT)以及募集型棕色脂肪(recruitable BAT, rBAT)。经典棕色脂肪存在于小鼠和人类婴儿肩胛区域，它的前体细胞与骨骼肌的前体细胞更加相似，是表达 *Myf5* 肌原性标记的前体细胞[10] [11]。募集型棕色脂肪在个体经运动或如长期冷暴露等产热刺激后产生于白色脂肪库和肌肉中，也被称为米色脂肪(Beige fat, Brite, brown-in-white)。米色脂肪与白色脂肪的前体相同，是不表达 *Myf5* 的前体细胞。白色脂肪转变为募集型棕色脂肪的过程被称为棕化[12]。而 Irisin 可以诱导白色脂肪发生棕化[1]。

Irisin 不仅可以由肌肉分泌，同时也可以从脂肪细胞中分泌[6]。人类白色脂肪组织中 *FNDC5* 表达量虽比肌肉中低 100~200 倍，但也构成了血浆中 Irisin 的一部分[13]。

4. Irisin 与运动的关系

FNDC5 mRNA 在运动后的啮齿动物模型[14]和人类[15]中都有表达。但运动对于血浆中 Irisin 水平的影响具有争议。最初研究者们对于运动促进人血液中 Irisin 水平增高得出不同的结论，同时指出不同种类的运动(耐力运动或抗阻运动，短期运动或长期运动)对血液 Irisin 水平有不同的影响，主要由于使用的抗体识别的是 FNDC5 的跨膜结构域，而不是识别被分泌的 Irisin [2] [16]。近年来，越来越多的研究者开始使用质谱测定血液中 Irisin 含量，从而使测定结果不受到不同抗体的影响[17] [18]。实验证明，耐力或抗阻运动都可以提高人类血液中 Irisin 的含量。

5. Irisin 在二型糖尿病中的作用

在 Bostrom 等最初发现 Irisin 的文章中指出，由于 Irisin 可以提高小鼠葡萄糖耐受，并降低空腹胰岛素水平，Irisin 的治疗潜力值得研究[1]。随后大量的研究开始探究 Irisin 在糖尿病中的作用。大部分研究显示二型糖尿病患者血液中 Irisin 含量降低[19] [20] [21]，若出现二型糖尿病的并发症，如：肾脏衰竭，心血管疾病，则 Irisin 含量更低[22] [23]。而在一型糖尿病中，Irisin 水平升高[24] [25]。同时，空腹血糖与 Irisin 含量呈正相关[15] [19] [26]，并且 Irisin 和胰岛 beta 细胞功能正相关[27]。

研究者们对于 Irisin 在孕期糖尿病患者中的含量具有争议。不同的研究者分别发现患有孕期糖尿病的女性血液中 Irisin 含量高于[28]，低于[29] [30] [31] [32] [33]，或相似于健康个体[34]。但是，绝大多数研究以及一个汇总分析[31]证明孕期糖尿病患者血浆中 Irisin 含量降低。

6. Irisin 在治疗中的作用

在糖尿病[35] [36]以及胰岛素抵抗[37] [38]小鼠模型中使用 Irisin 可以通过调节 AMPK 信号通路[37]降低糖异生作用，促进糖原生成，改善肌肉胰岛素抵抗。Irisin 还可以增强糖尿病小鼠内皮细胞功能[39]。Irisin 同样可以抑制由高糖[40]或高饱和脂肪酸饮食[41]引起的凋亡而增强胰岛 β 细胞存活率。由于外源 Irisin 可有效地使皮下脂肪棕化，理论上还可以将其制成可注射的多肽辅助治疗肥胖，糖尿病等代谢疾病[1]。

7. Irisin 还是 FNDC5?

Irisin 从其被发现开始就被广泛的研究，而它的前体 FNDC5 却被相对较少的人关注。FNDC5 在新陈代谢[42] [43]，心肌细胞分化[44] [45]，神经发育[46] [47]中具有重要作用。而 *FNDC5* 的基因多态性在人群中与很多疾病相关：如 *FNDC5* 单核苷酸多态性 rs16835198 和 rs726344 在 1976 个德国受试者中和胰岛素敏感性显著相关($p < 0.0253$) [48]，rs16835198 在一项对 6822 名中国汉族人的基因型筛查中显示和空腹胰岛素水平显著相关($p < 0.046$) [49]。

8. Irisin 在神经系统中的作用

Irisin 在神经系统的发育中具有重要作用。FNDC5 基因在脑的很多区域都有表达，如：小脑浦肯野细胞[3]，下丘脑[50]以及海马体[51]。Western 以及质谱证明 Irisin 在脑脊液中也存在[28] [52]。在原代小鼠胚胎大脑皮层神经元细胞成熟过程中，以及人类胚胎干细胞来源的神经细胞分化为神经元的过程中，FNDC5 含量升高[46] [51]。FNDC5 过表达促进小鼠胚胎干细胞向神经细胞的分化[53]，而 FNDC5 knockdown 显著抑制小鼠胚胎干细胞向神经细胞的分化[54]。

Irisin 介导了运动对脑健康的有益作用。运动对脑健康具有很多益处，如降低痴呆和抑郁的风险，维护认知能力。而运动对于脑神经系统的作用很可能是由肌肉分泌的激素进入血液，通过血脑屏障而引起脑中基因表达的改变。PGC1a-FNDC5-BDNF 通路的发现就为此提供了有力的证据。BDNF (Brain-derived neurotrophic factor)是介导由运动引起的海马齿状回细胞增殖的重要因子[55]。运动引起肌肉中 PGC1a 蛋白表达量升高[56]，而 PGC1a 促进 *FNDC5* 表达[1]。使用腺病毒载体在肝脏中表达 FNDC5 可以提高血浆中 Irisin 含量，并导致海马 *BDNF* 表达量升高。后期，由研究者发现，耐力运动不仅可以提高骨骼肌中 *Irisin* 表达量，还可以提高海马中 *Irisin* 的表达量[51]。

随后几项研究探索了衰老个体[57]，年轻运动员[58]或肥胖症患者[59]血浆中 Irisin 含量和认知功能的关系。其中两项研究表明 Irisin 与更好的认知功能相关[57] [58]，而另外的一项研究发现 Irisin 与认知功能负相关[59]。

9. 亟待解决的问题

自从 Irisin 在 2012 年被发现，研究者们对于 Irisin 产生了浓厚的兴趣；使用 Irisin 这一关键词在 PubMed 上搜索即可得到超过 1000 篇同行评审期刊上的文章。Irisin 对于很多系统都具有重要的生理作用，如：糖代谢稳定，白色脂肪棕化，神经系统发育等。但是有关 Irisin 的研究也存在许多尚未解决的问题。

从上综述可以发现，关于 Irisin 的研究有很多出入，甚至结论完全相反，其中一个重要原因就是不同研究者使用的抗体或实验方法不同。人血浆中 Irisin 含量就有 0.01 ng/ml 到 2000 ng/ml 范围之内的不同报道[60] [61] [62] [63] [64]，这说明将样品制备步骤标准化，以及探测 Irisin 含量方法的统一化至关重要。

最初发现 Irisin 的文章中使用的抗体是识别 FNDC5 疏水结构域和 C 末端的抗体[1]，所以其中被认为是 Irisin 的条带可能是全长 FNDC5 或其他被非特异识别的蛋白。随后，识别 Irisin 纤维连接蛋白 III 结构域的抗体进入市场被广泛使用。可见，Irisin 相关研究中使用的抗体也是比较研究结果之间差别的重要因素。如果样品制备步骤，使用的抗体，检测的方法不同，那么不同研究之间很难有可比性。而这也是 Irisin 相关生理效应研究的一个难点。

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参考文献

[1] Bostrom, P., *et al*. (2012) A PGC1-Alpha-Dependent Myokine That Drives Brown-Fat-Like Development of White Fat and Thermogenesis. *Nature*, **481**, 463-468. https://doi.org/10.1038/nature10777

[2] Huh, J.Y., *et al*. (2014) Irisin in Response to Acute and Chronic Whole-Body Vibration Exercise in Humans. *Metabolism*, **63**, 918-921. https://doi.org/10.1016/j.metabol.2014.04.001

[3] Dun, S.L., *et al*. (2013) Irisin-Immunoreactivity in Neural and Non-Neural Cells of the Rodent. *Neuroscience*, **240**, 155-162. https://doi.org/10.1016/j.neuroscience.2013.02.050

[4] Aydin, S., *et al*. (2015) Effect of Carnosine Supplementation on Apoptosis and Irisin, Total Oxidant and Antioxidants Levels in the Serum, Liver and Lung Tissues in Rats Exposed to Formaldehyde Inhalation. *Peptides*, **64**, 14-23. https://doi.org/10.1016/j.peptides.2014.11.008

[5] Moreno-Navarrete, J.M., *et al*. (2013) Irisin Is Expressed and Produced by Human Muscle and Adipose Tissue in Association with Obesity and Insulin Resistance. *The Journal of Clinical Endocrinology and Metabolism*, **98**, E769-E778. https://doi.org/10.1210/jc.2012-2749

[6] Roca-Rivada, A., *et al*. (2013) FNDC5/Irisin Is Not Only a Myokine But Also an Adipokine. *PLoS ONE*, **8**, e60563. https://doi.org/10.1371/journal.pone.0060563

[7] Aydin, S., *et al*. (2014) A Comprehensive Immunohistochemical Examination of the Distribution of the Fat-Burning Protein Irisin in Biological Tissues. *Peptides*, **61**, 130-136. https://doi.org/10.1016/j.peptides.2014.09.014

[8] Giralt, M. and Villarroya, F. (2013) White, Brown, Beige/Brite: Different Adipose Cells for Different Functions? *Endocrinology*, **154**, 2992-3000. https://doi.org/10.1210/en.2013-1403

[9] Jastroch, M., *et al*. (2010) Mitochondrial Proton and Electron Leaks. *Essays in Biochemistry*, **47**, 53-67. https://doi.org/10.1042/bse0470053

[10] Seale, P., *et al*. (2008) PRDM16 Controls a Brown Fat/Skeletal Muscle Switch. *Nature*, **454**, 961-967. https://doi.org/10.1038/nature07182

[11] Timmons, J.A., *et al*. (2007) Myogenic Gene Expression Signature Establishes That Brown and White Adipocytes Originate from Distinct Cell Lineages. *Proceedings of the National Academy of Sciences of the United States of America*, **104**, 4401-4406. https://doi.org/10.1073/pnas.0610615104

[12] Young, P., Arch, J.R. and Ashwell, M. (1984) Brown Adipose Tissue in the Parametrial Fat Pad of the Mouse. *FEBS Letters*, **167**, 10-14. https://doi.org/10.1016/0014-5793(84)80822-4

[13] Perakakis, N., *et al*. (2017) Physiology and Role of Irisin in Glucose Homeostasis. *Nature Reviews Endocrinology*, **13**, 324-337. https://doi.org/10.1038/nrendo.2016.221

[14] Roberts, M.D., *et al*. (2013) Elevated Skeletal Muscle Irisin Precursor FNDC5 mRNA in Obese OLETF Rats. *Metabolism*, **62**, 1052-1056. https://doi.org/10.1016/j.metabol.2013.02.002

[15] Huh, J.Y., *et al*. (2012) FNDC5 and Irisin in Humans: I. Predictors of Circulating Concentrations in Serum and Plasma and II. mRNA Expression and Circulating Concentrations in Response to Weight Loss and Exercise. *Metabolism*, **61**, 1725-1738. https://doi.org/10.1016/j.metabol.2012.09.002

[16] Ellefsen, S., *et al*. (2014) Irisin and FNDC5: Effects of 12-Week Strength Training, and Relations to Muscle Phenotype and Body Mass Composition in Untrained Women. *European Journal of Applied Physiology*, **114**, 1875-1888. https://doi.org/10.1007/s00421-014-2922-x

[17] Daskalopoulou, S.S., *et al*. (2014) Plasma Irisin Levels Progressively Increase in Response to Increasing Exercise Workloads in Young, Healthy, Active Subjects. *European Journal of Endocrinology*, **171**, 343-352. https://doi.org/10.1530/EJE-14-0204

[18] Jedrychowski, M.P., *et al*. (2015) Detection and Quantitation of Circulating Human Irisin by Tandem Mass Spectrometry. *Cell Metabolism*, **22**, 734-740. https://doi.org/10.1016/j.cmet.2015.08.001

[19] Liu, J.J., *et al*. (2013) Lower Circulating Irisin Is Associated with Type 2 Diabetes Mellitus. *Journal of Diabetic Complications*, **27**, 365-369. https://doi.org/10.1016/j.jdiacomp.2013.03.002

[20] Choi, Y.K., *et al*. (2013) Serum Irisin Levels in New-Onset Type 2 Diabetes. *Diabetes Research and Clinical Practice*, **100**, 96-101. https://doi.org/10.1016/j.diabres.2013.01.007

[21] Kurdiova, T., *et al*. (2014) Effects of Obesity, Diabetes and Exercise on Fndc5 Gene Expression and Irisin Release in Human Skeletal Muscle and Adipose Tissue: *In Vivo* and *in Vitro* Studies. *The Journal of Physiology*, **592**, 1091-1107. https://doi.org/10.1113/jphysiol.2013.264655

[22] Zhang, M., *et al*. (2014) The Association of New Inflammatory Markers with Type 2 Diabetes Mellitus and Macrovascular Complications: A Preliminary Study. *European Review for Medical and Pharmacological Sciences*, **18**, 1567-1572.

[23] Liu, J.J., *et al*. (2014) Relationship between Circulating Irisin, Renal Function and Body Composition in Type 2 Diabetes. *Journal of Diabetic Complications*, **28**, 208-213. https://doi.org/10.1016/j.jdiacomp.2013.09.011

[24] Ates, I., *et al*. (2017) Factors Associated with Increased Irisin Levels in the Type 1 Diabetes Mellitus. *Endocrine Regulations*, **51**, 1-7. https://doi.org/10.1515/enr-2017-0001

[25] Espes, D., Lau, J. and Carlsson, P.O. (2015) Increased Levels of Irisin in People with Long-Standing Type 1 Diabetes. *Diabetic Medicine*, **32**, 1172-1176. https://doi.org/10.1111/dme.12731

[26] Huerta, A.E., *et al*. (2015) Circulating Irisin and Glucose Metabolism in Overweight/Obese Women: Effects of Alpha-Lipoic Acid and Eicosapentaenoic Acid. *Journal of Physiology and Biochemistry*, **71**, 547-558. https://doi.org/10.1007/s13105-015-0400-5

[27] Yang, M., *et al*. (2014) Circulating Levels of Irisin in Middle-Aged First-Degree Relatives of Type 2 Diabetes Mellitus—Correlation with Pancreatic Beta-Cell Function. *Diabetology & Metabolic Syndrome*, **6**, 133. https://doi.org/10.1186/1758-5996-6-133

[28] Piya, M.K., *et al*. (2014) The Identification of Irisin in Human Cerebrospinal Fluid: Influence of Adiposity, Metabolic Markers, and Gestational Diabetes. *American Journal of Physiology-Endocrinology and Metabolism*, **306**, E512-E518. https://doi.org/10.1152/ajpendo.00308.2013

[29] Kuzmicki, M., *et al*. (2014) Serum Irisin Concentration in Women with Gestational Diabetes. *Gynecological Endocrinology*, **30**, 636-639. https://doi.org/10.3109/09513590.2014.920006

[30] Usluogullari, B., *et al*. (2017) Role of Serum Levels of Irisin and Oxidative Stress Markers in Pregnant Women with and without Gestational Diabetes. *Gynecological Endocrinology*, **33**, 405-407. https://doi.org/10.1080/09513590.2017.1284789

[31] Zhao, L., *et al*. (2015) Circulating Irisin Is Lower in Gestational Diabetes Mellitus. *Endocrine Journal*, **62**, 921-926. https://doi.org/10.1507/endocrj.EJ15-0230

[32] Yuksel, M.A., *et al*. (2014) Maternal Serum and Fetal Cord Blood Irisin Levels in Gestational Diabetes Mellitus. *Diabetes Research and Clinical Practice*, **104**, 171-175. https://doi.org/10.1016/j.diabres.2013.12.025

[33] Ural, U.M., *et al*. (2016) Alteration of Maternal Serum Irisin Levels in Gestational Diabetes Mellitus. *Ginekologia Polska*, **87**, 395-398. https://doi.org/10.5603/GP.2016.0013

[34] Ebert, T., *et al*. (2014) Serum Levels of Irisin in Gestational Diabetes Mellitus during Pregnancy and after Delivery. *Cytokine*, **65**, 153-158. https://doi.org/10.1016/j.cyto.2013.11.009

[35] Liu, T.Y., *et al*. (2015) Irisin Inhibits Hepatic Gluconeogenesis and Increases Glycogen Synthesis via the PI3K/Akt Pathway in Type 2 Diabetic Mice and Hepatocytes. *Clinical Science*, **129**, 839-850. https://doi.org/10.1042/CS20150009

[36] Duan, H., *et al*. (2016) Anti-Diabetic Activity of Recombinant Irisin in STZ-Induced Insulin-Deficient Diabetic Mice. *International Journal of Biological Macromolecules*, **84**, 457-463. https://doi.org/10.1016/j.ijbiomac.2015.12.049

[37] Xin, C., *et al*. (2016) Irisin Improves Fatty Acid Oxidation and Glucose Utilization in Type 2 Diabetes by Regulating the AMPK Signaling Pathway. *International Journal of Obesity* (*London*), **40**, 443-451. https://doi.org/10.1038/ijo.2015.199

[38] Yang, Z., *et al*. (2015) Decreased Irisin Secretion Contributes to Muscle Insulin Resistance in High-Fat Diet Mice. *International Journal of Clinical and Experimental Pathology*, **8**, 6490-6497.

[39] Zhu, D., *et al*. (2015) Irisin Improves Endothelial Function in Type 2 Diabetes through Reducing Oxidative/Nitrative Stresses. *Journal of Molecular and Cellular Cardiology*, **87**, 138-147. https://doi.org/10.1016/j.yjmcc.2015.07.015

[40] Liu, S., *et al*. (2017) Effects and Underlying Mechanisms of Irisin on the Proliferation and Apoptosis of Pancreatic Beta Cells. *PLoS ONE*, **12**, e0175498. https://doi.org/10.1371/journal.pone.0175498

[41] Natalicchio, A., *et al*. (2017) The Myokine Irisin Is Released in Response to Saturated Fatty Acids and Promotes Pancreatic Beta-Cell Survival and Insulin Secretion. *Diabetes*, **66**, 2849-2856. https://doi.org/10.2337/db17-0002

[42] Cai, C., *et al*. (2017) Gene Location, Expression, and Function of FNDC5 in Meishan Pigs. *Scientific Reports*, **7**, Article No. 7886. https://doi.org/10.1038/s41598-017-08406-y

[43] Xiong, X.Q., *et al*. (2015) FNDC5 Overexpression and Irisin Ameliorate Glucose/Lipid Metabolic Derangements and Enhance Lipolysis in Obesity. *Biochimica et Biophysica Acta*, **1852**, 1867-1875. https://doi.org/10.1016/j.bbadis.2015.06.017

[44] Rabiee, F., *et al*. (2014) Induced Expression of Fndc5 Significantly Increased Cardiomyocyte Differentiation Rate of Mouse Embryonic Stem Cells. *Gene*, **551**, 127-137. https://doi.org/10.1016/j.gene.2014.08.045

[45] Nazem, S., *et al*. (2018) Fndc5 Knockdown Induced Suppression of Mitochondrial Integrity and Significantly Decreased Cardiac Differentiation of Mouse Embryonic Stem Cells. *Journal of Cellular Biochemistry*, **119**, 4528-4539. https://doi.org/10.1002/jcb.26590

[46] Ghahrizjani, F.A., *et al*. (2015) Enhanced Expression of FNDC5 in Human Embryonic Stem Cell-Derived Neural Cells Along with Relevant Embryonic Neural Tissues. *Gene*, **557**, 123-129. https://doi.org/10.1016/j.gene.2014.12.010

[47] Tanhaei, S., *et al*. (2018) RNA/Protein Discordant Expression of Fndc5 in Central Nervous System Is Likely to Be Mediated through microRNAs. *DNA and Cell Biology*, **37**, 373-380. https://doi.org/10.1089/dna.2017.4067

[48] Staiger, H., *et al*. (2013) Common Genetic Variation in the Human FNDC5 Locus, Encoding the Novel Mus-

cle-Derived “Browning” Factor Irisin, Determines Insulin Sensitivity. *PLoS ONE*, **8**, e61903. https://doi.org/10.1371/journal.pone.0061903

[49] Tang, S., *et al*. (2014) An Interaction between a FNDC5 Variant and Obesity Modulates Glucose Metabolism in a Chinese Han Population. *PLoS ONE*, **9**, e109957. https://doi.org/10.1371/journal.pone.0109957

[50] Varela-Rodriguez, B.M., *et al*. (2016) FNDC5 Expression and Circulating Irisin Levels Are Modified by Diet and Hormonal Conditions in Hypothalamus, Adipose Tissue and Muscle. *Scientific Reports*, **6**, Article No. 29898. https://doi.org/10.1038/srep29898

[51] Wrann, C.D., *et al*. (2013) Exercise Induces Hippocampal BDNF through a PGC-1alpha/FNDC5 Pathway. *Cell Metabolism*, **18**, 649-659. https://doi.org/10.1016/j.cmet.2013.09.008

[52] Ruan, Q., *et al*. (2018) Detection and Quantitation of Irisin in Human Cerebrospinal Fluid by Tandem Mass Spectrometry. *Peptides*, **103**, 60-64. https://doi.org/10.1016/j.peptides.2018.03.013

[53] Forouzanfar, M., *et al*. (2015) Fndc5 Overexpression Facilitated Neural Differentiation of Mouse Embryonic Stem Cells. *Cell Biology International*, **39**, 629-637. https://doi.org/10.1002/cbin.10427

[54] Hashemi, M.S., *et al*. (2013) Fndc5 Knockdown Significantly Decreased Neural Differentiation Rate of Mouse Embryonic Stem Cells. *Neuroscience*, **231**, 296-304. https://doi.org/10.1016/j.neuroscience.2012.11.041

[55] Vaynman, S., Ying, Z. and Gomez-Pinilla, F. (2004) Hippocampal BDNF Mediates the Efficacy of Exercise on Synaptic Plasticity and Cognition. *European Journal of Neuroscience*, **20**, 2580-2590. https://doi.org/10.1111/j.1460-9568.2004.03720.x

[56] Olesen, J., Kiilerich, K. and Pilegaard, H. (2010) PGC-1alpha-Mediated Adaptations in Skeletal Muscle. *Pflügers Archiv*, **460**, 153-162. https://doi.org/10.1007/s00424-010-0834-0

[57] Kuster, O.C., *et al*. (2017) Novel Blood-Based Biomarkers of Cognition, Stress, and Physical or Cognitive Training in Older Adults at Risk of Dementia: Preliminary Evidence for a Role of BDNF, Irisin, and the Kynurenine Pathway. *Journal of Alzheimer's Disease*, **59**, 1097-1111. https://doi.org/10.3233/JAD-170447

[58] Belviranli, M., *et al*. (2016) The Relationship between Brain-Derived Neurotrophic Factor, Irisin and Cognitive Skills of Endurance Athletes. *The Physician and Sportsmedicine*, **44**, 290-296. https://doi.org/10.1080/00913847.2016.1196125

[59] Fagundo, A.B., *et al*. (2016) Modulation of Irisin and Physical Activity on Executive Functions in Obesity and Morbid Obesity. *Scientific Reports*, **6**, Article No. 30820. https://doi.org/10.1038/srep30820

[60] Crujeiras, A.B., Pardo, M. and Casanueva, F.F. (2015) Irisin: “Fat” or Artefact. *Clinical Endocrinology*, **82**, 467-474. https://doi.org/10.1111/cen.12627

[61] Elbelt, U., Hofmann, T. and Stengel, A. (2013) Irisin: What Promise Does It Hold? *Current Opinion in Clinical Nutrition & Metabolic Care*, **16**, 541-547. https://doi.org/10.1097/MCO.0b013e328363bc65

[62] Hofmann, T., Elbelt, U. and Stengel, A. (2014) Irisin as a Muscle-Derived Hormone Stimulating Thermogenesis—A Critical Update. *Peptides*, **54**, 89-100. https://doi.org/10.1016/j.peptides.2014.01.016

[63] Polyzos, S.A. and Mantzoros, C.S. (2015) An Update on the Validity of Irisin Assays and the Link between Irisin and Hepatic Metabolism. *Metabolism*, **64**, 937-942. https://doi.org/10.1016/j.metabol.2015.06.005

[64] Polyzos, S.A., Mathew, H. and Mantzoros, C.S. (2015) Irisin: A True, Circulating Hormone. *Metabolism*, **64**, 1611-1618. https://doi.org/10.1016/j.metabol.2015.09.001