Advances in Clinical Medicine 临床医学进展, 2025, 15(1), 947-953
Published Online January 2025 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2025.151126

Hans汉斯

O-GlcNAc糖基化修饰在癌症中的调控机制

周美欣[1]，刘　桐[2*]，薛　娟[1*]

[1]西海岸新区区立医院口腔科，山东　青岛
[2]青岛大学附属泰安市中心医院口腔科，山东　泰安

收稿日期：2024年12月15日；录用日期：2025年1月8日；发布日期：2025年1月20日

摘　要

O-GlcNAc糖基化是一种可逆的蛋白质翻译后修饰。O-GlcNAc循环失衡在癌症的发生和发展中起着至关重要的作用。因此，探索O-GlcNAc糖基化与肿瘤之间的作用机制对于开发新的靶向治疗方法具有极其重要的意义。本文阐明O-GlcNAc糖基化修饰使细胞能够将营养物质的可用性和细胞代谢与关键细胞过程调节联系起来，其中许多可能在癌症中受到损害。总结O-GlcNAc糖基化调节在肿瘤治疗中的作用，为临床实践中开发新的靶向疗法提供了理论依据。

关键词

O-GlcNAc糖基化，分子机制，预后

The Regulatory Mechanism of O-GlcNAc Glycosylation Modification in Cancer

Meixin Zhou[1], Tong Liu[2*], Juan Xue[1*]

[1]Department of Stomatology, West Coast New Area District Hospital, Qingdao Shandong
[2]Department of Stomatology, Tai'an Central Hospital Affiliated to Qingdao University, Tai'an Shandong

Received: Dec. 15th, 2024; accepted: Jan. 8th, 2025; published: Jan. 20th, 2025

Abstract

O-GlcNAc glycosylation is a reversible post-translational modification of proteins. The imbalance of O-GlcNAc cycle plays a crucial role in the occurrence and development of cancer. Therefore, exploring the mechanism of action between O-GlcNAc glycosylation and tumors is of great significance for developing new targeted therapies. This article elucidates that O-GlcNAc glycosylation modification enables cells to link the availability of nutrients and cellular metabolism with the regulation of key

*通讯作者。

文章引用: 周美欣, 刘桐, 薛娟. O-GlcNAc 糖基化修饰在癌症中的调控机制[J]. 临床医学进展, 2025, 15(1): 947-953.
DOI: 10.12677/acm.2025.151126

cellular processes, many of which may be compromised in cancer. Summarizing the role of O-GlcNAc glycosylation regulation in tumor therapy provides a theoretical basis for the development of new targeted therapies in clinical practice.

Keywords

O-GlcNAc Glycosylation, Molecular Mechanism, Prognosis

1. 前言

O-连接的 N-乙酰氨基葡萄糖基化(O-GlcNAcylation)是一种可逆的蛋白质翻译后修饰(PTM)，主要调节蛋白质酶活性[1]、亚细胞定位、蛋白质稳定性、转录活性以及与其他蛋白质的相互作用[2]。到目前为止，大约有 3000 种人类蛋白质被证实是 O-GlcNAc 糖基化[3]。O-GlcNAcylation 循环障碍与各种慢性人类疾病的进展有关，包括衰老、肥胖、糖尿病、心血管疾病、神经退行性疾病和癌症[4]。近年来，O-GlcNAc 糖基化已被报道与肿瘤的发展密切相关[5]。在不同类型的癌症中发现 O-GlcNAcylation 水平失衡[6]，导致各种癌症标志物，如肿瘤生长、转移、血管生成、癌症干燥潜能和代谢重编程[7]。因此，探索 O-GlcNAc 糖基化在肿瘤中的具体机制具有重要意义。

在这篇文章中，我们主要关注 O-GlcNAcylation 与癌症相关炎症之间关系的最新研究，并概述 O-GlcNAcylation 如何驱动肿瘤的潜在机制及其与癌症进展的关系。

2. O-GlcNAc 糖基化：一种特殊的糖基化修饰

糖基化是将寡糖化合物附着到蛋白质上以产生糖蛋白的过程[8]。它形成了 PTM 的一种常见形式，包括 n-聚糖[9]、邻聚糖和蛋白多糖。O-GlcNAc 糖基化不同于 N-糖基化和其他 O-糖基化，主要发生在核蛋白[10]、细胞质蛋白和线粒体蛋白上。O-GlcNAc 糖基化是一种非典型糖基化，涉及单个 O-链 N-乙酰葡糖胺(O-GlcNAc)部分附着在细胞质[11]、细胞核和线粒体中的丝氨酸和苏氨酸残基上。O-GlcNAc 糖基化是通过己糖胺生物合成途径(HBP)产生营养物质的产物，该途径结合了葡萄糖[12]、氨基酸、脂肪酸和核苷酸代谢，产生清除 O-GlcA 酰化的供体底物尿苷二磷酸 GlcNAc [13]。除了依赖营养物质的可用性外，O-GlcNAc 信号通路对细胞应激也高度敏感[14]。O-GlcNAc 糖基化被认为是一种营养和应激传感器，调节从转录和翻译到信号转导和代谢的细胞过程。

OGT 和 OGA 是唯一控制 O-GlcNAc 循环的酶[15]。OGT 和 OGA 可以通过选择性剪接和选择性起始密码子产生多种亚型[16]。在饥饿或其他压力条件下，OGT 和 OGA 会发生复杂的变化[17]，它们在细胞中的丰度和活性也会发生变化。当 O-GlcNAc 水平升高时，OGT 的 mRNA 成熟被阻断[18]，而 OGA 的成熟被促进，导致 OGA 增加和 OGT 减少。相比之下，低水平的 O-GlcNAc 促进 OGT mRNA 成熟并抑制 OGA [19]。OGT 形成具有重要功能的剪刀形二聚体。在 OGT-OGA 的复杂结构中，一个长而可行的 OGA 片段占据了延伸 OGT 的底物结合槽，并定位了一个丝氨酸进行 O-GlcNA 酰化[20]，从而防止 OGT 修饰其他底物。相比之下，OGT 会破坏 OGA 的选择性二聚化并阻断其活性位点[21]，从而阻断其他底物的进入[22]。

3. O-GlcNAc 酰化和炎症相关信号通路

3.1. NF-κB 通路

核因子(NF)-κB 转录因子家族由五种蛋白质组成[23]，包括 p65 (RelA)、RelB、cRel 和 p105/p50 (NF-κB1)以及 p100/p52 (NF-κB2) [24]。NF-κB 活性与肿瘤的发病机制密切相关，主要受 PTMs 调节[25]，如磷酸化、乙酰化和糖基化。NF-κB 调节多种细胞过程，如先天免疫、适应性免疫[26]、炎症、细胞凋亡、细胞存活和分化，其激活在炎症和免疫反应中起着核心作用。NF-kB 可以被各种刺激激活，如脂多糖(LPS)和葡萄糖[27]。活化的 IKK 复合物介导 IkB 的磷酸化以降解蛋白酶体[28]。游离的 NF-κB 从细胞质转移到细胞核，与 DNA 元件结合并激活靶基因的表达[29]。此外，位点特异性 O-GlcNAc 与 NF-κB 途径介导的炎症有关[30]。NF-κB 中 p65 的 O-GlcNAcThr352 减少了其与 IkB 的结合，IkB 是高血糖条件下转录活性所必需的[31]。NF-κB 信号通路的活性可能通过 OGT 介导的 O-GlcN 酰化间接调节[32]。糖皮质激素受体(GR)可以与 NF-κB 家族成员相互作用并抑制其功能，包括大量促炎蛋白 NF-κB 下游基因的转录，如白细胞介素-8 (IL-8)和细胞内粘附分子-1 (ICAM-1) [33]。最近的一项研究表明，OGT 通过增强聚合酶(pol) II CTD 的 O-GlcNA 酰化来促进 NF-κB [34]，这反过来又破坏了肿瘤坏死因子(TNF)-α 诱导的 pol II CTD 磷酸化，并进一步阻碍了 IL-8 和 ICAM-1 的转录起始阶段[35]。

3.2. JAK-STAT 通路

Janus 激酶/信号转导子和信号转换转录激活子(JAK-STAT)信号通路参与致癌过程中调节细胞因子依赖性炎症和免疫，激活 JAK 和 STAT3 [36]，并转运 STAT3 以转录靶基因，如 IL-10 [37]。Li 等人最近发现，STAT3 在 T717 位点被 o-glcn 酰化，抑制 STAT3 的转录活性和下游基因的表达。T717 位点突变阻止了 STAT3 的 O-GlcNA 酰化，并显著增强了其磷酸化和转录活性[37]。Stat3-O-GlcNAcylization 受 Culin-3 (CUL3)的负调控[38]。CUL3 缺乏可以通过促进核因子重组蛋白 2-相关因子 2 (Nrf2)的稳定性和巨噬细胞的酰化水平来增强 OGT 和总蛋白 O-GlcN 的表达，Nrf2 是 OGT 转录调节因子。与野生型细胞相比，CUL3 缺乏的巨噬细胞中靶基因(如 IL-10)的水平和表达水平有所降低[39]。这一发现进一步揭示了过度免疫炎症激活诱导的 IL-6 如何调节 STAT3-O-GlcNA 酰化。

STAT6 是 STAT 家族的另一个成员[40]，其转录激活主要是由 IL-4 和 IL-13 与其各自受体的结合诱导的[41]。OGT 介导的 STAT6 O-GlcNA 酰化在蠕虫感染期间促进了 STAT6 的转录活性，并进一步促进了 Pou2f3 和 Gsdmc 的转录[42]。STAT6 O-GlcNacylization 介导的蛋白质增加了 POU2F3 驱动的树突状细胞的分化，促进了抗蠕虫细胞因子 IL-25 [43]的释放。此外，GSDMC 介导无细胞 GSDMCN 孔的形成，以分泌 IL-33。重要的是，肠上皮细胞(IEC)分泌 IL-25 和 IL-33 已被证明可以促进第二组先天淋巴细胞(ILC2)和 CD4+T 辅助细胞 2 (Th2)细胞产生 2 型细胞因子[44]，如 IL-13 和 IL-4 [45]。这引发了蠕虫排泄和耐受的 2 型免疫反应[46]。随后，鉴定了 STAT6 位点的 O-GlcNA 酰化，证实了反向结构域内的五个位点(S746、T757、S778、S810 和 S825)构成了关键的 O-Glc 酰化位点。所有五个位点突变为丙氨酸完全取消了 STAT6 的 O-GlcNA 酰化水平，降低了其转录活性，并降低了 STAT6 下调的转录靶基因 Pou2f3 和 Gsdmc。这进一步抑制了 IEC 产生和分泌 IL-25 和 IL-33，最终损害了抗蠕虫 2 型免疫反应[46]。OGT 对多个 STAT6 位点 O-GlcNA 酰化的调节对于驱动针对蠕虫感染的 2 型免疫反应至关重要[46]。

4. O-GlcNAc 在癌症治疗中的相互作用

4.1. 肺癌

肺癌是全球主要的健康威胁，也是全球癌症相关发病率和死亡率的主要原因。2018 年，约有 209 万

例新诊断的肺癌[47]。传统的治疗方法如放疗和化疗通常疗效有限，特别是对于中晚期肺癌患者，他们通常死亡率高，预后差。尽管如此，最近在靶向治疗和免疫疗法方面的进展还是带来了新的希望。尽管有了这些进展，但随着时间的推移，许多患者对这些治疗产生了耐药性。因此，了解肺癌获得性耐药的分子机制至关重要。最近的研究强调了 O-GlcNAc 酰化在注入肺癌耐药性中的重要作用。例如，超 O-GlcNAc 酰化可以通过涉及 p53 或 c-Myc 的不同机制使肺癌细胞抵抗凋亡，这取决于细胞环境[48]。高 CDDpin 诱导的 p53 激活，超 O-GlcNAc 酰化靶向 p53，促进其泛素化和随后的 p53 降解，从而获得致癌和抗凋亡功能。与 p53 激活率低相比，高 O-GlcNAc 酰化对 p53 的影响最小，而是通过干扰其泛素介导的降解来调节 c-Myc 的稳定性[49]。在顺铂治疗期间，O-GlcNAc 酰化与 p53 或 c-霉素化和泛素化之间的相关性分析支持了这些观点。

4.2. 胶质瘤

胶质瘤是最常见的恶性脑肿瘤类型，多形性胶质母细胞瘤特别具有侵袭性，常致命，导致患者预后较差[50]。虽然导致胶质瘤发展和进展的确切机制尚不清楚，但最近的研究提供了一些线索。Xu 等人报道，亲黑素的 O-GlcNAc 酰化(MLPH)通过与含有 21 的 E3 泛素连接酶三部分基序(TRIM21)相互作用来阻止其降解。Tis 相互作用似乎通过激活 NF-κB 信号通路[51]来增强胶质母细胞瘤对辐射的抵抗力。另一项研究强调了 zeste 同源物 2 (EZH2)增强子在控制胶质瘤抗肿瘤免疫中的作用。EZH2 的结构有利于磷酸化和 O-GlcNAc 酰化，促进胶质瘤细胞的侵袭和转移。抑制 EZH2 表达和经前颅磁刺激可能逆转胶质瘤患者对替莫唑胺的耐药性

4.3. 乳腺癌

乳腺癌 BC 约占全球女性所有癌症的 30%，死亡率显著为 15%。随着全球发病率和死亡率的逐年增长，确定有效的生物标志物的 BC 诊断和预后是至关重要的。沉默信息调节因子 1 (SIRT1)是一种 NAD+依赖的去乙酰化酶，在 BC [52]中起重要作用。例如，Ferrer 等人证实了 SIRT1 在 OGT 介导的叉头盒 M1 (FOXM1)泛素化调控中的关键作用，表明降低 SIRT1 活性可以减轻 OGT 对 FOXM1 的影响，从而注入 BC 细胞[52]的侵袭和转移。进一步的研究表明，利亚诺定受体 1 (RYR1)的 O-GlcNAc 酰化干扰 nek10 介导的磷酸化，增加泛素化和蛋白酶体降解；miR-122 介导的 OGT 减少导致 BC 中 RYR1 丰度升高。此外，Yang 等人发现 MCF-7 细胞中 p53Ser149 位点的 O-GlcNAc 酰化降低了 Tr 155 的磷酸化，使 p53 部分抵抗链脲佐菌素处理[53]下的泛素依赖的蛋白水解，影响了细胞活力。Tesefns 强调了癌症治疗中 O-GlcNAc 酰化、磷酸化和泛素化之间存在复杂的相互作用，强调需要进一步研究突变蛋白与 O-GlcNAc 酰化之间的关系，特别是 p53 调控和 O-GlcNac 酰化。

5. 结论和未来展望

O-GlcNAc 修饰是细胞对各种刺激作出反应的关键机制。O-GlcNAc 修饰使细胞能够将营养物质的可用性和细胞代谢与关键细胞过程的调节联系起来，其中许多可能在癌症中受到损害。O-GlcNA 酰化的改变是调节细胞周期进程、适应局部环境和基因表达变化的机制之一。O-GlcNA 酰化的变化也会破坏其他信号系统的信息流，如磷酸化、泛素化和乙酰化。

O-GlcNAc 糖基化是一种新的非经典糖基化反应[5]。尽管有足够的证据表明 O-GlcNA 酰化在调节肿瘤炎症中起着关键作用，但其机制仍有待充分阐明。OGT 和 OGA 的调节和靶向对于维持正常的细胞功能至关重要，这些酶靶向其众多底物的机制仍有待阐明[2]。尽管人类癌症与 OGT 或 OGA 突变之间没有直接相关性，这可能是由于这些突变的致命性，但这两种酶的调节变化对细胞功能有着深远的影响。抑

制 OGT 或 OGA 的靶向化疗药物可能会改变肿瘤功能，或使肿瘤更容易受到其他作用或化疗药物的影响[5]。然而，抑制 OGT 或 OGA 对正常细胞的潜在不利影响尚不清楚。最近，产生了一种 O-GlcNAc 传感器蛋白，并在信号转导过程中表现出动态的 O-GlcNAc 糖基化。这项技术将允许在体内仔细分析不同信号系统对 O-GlcNAc 循环的影响[7]。使用深度测序和先进的蛋白质组学技术的研究，如稳定的氨基酸同位素标记或细胞培养中的相对和绝对定量，将为 O-GlcNAc 调节的信号通路提供新的见解。更好地了解与癌症变化相关的途径以及 O-GlcNAc 在这些途径中的作用，将有助于开发新的靶向治疗方法。

基金项目

本项目受泰安市科技创新发展项目(2023NS246)支持。

参考文献

[1] Olsen, J.V. and Mann, M. (2013) Status of Large-Scale Analysis of Post-Translational Modifications by Mass Spectrometry. *Molecular & Cellular Proteomics*, **12**, 3444-3452. https://doi.org/10.1074/mcp.o113.034181

[2] Yang, X. and Qian, K. (2017) Protein *O*-GlcNAcylation: Emerging Mechanisms and Functions. *Nature Reviews Molecular Cell Biology*, **18**, 452-465. https://doi.org/10.1038/nrm.2017.22

[3] Whelan, S.A. and Hart, G.W. (2003) Proteomic Approaches to Analyze the Dynamic Relationships between Nucleocytoplasmic Protein Glycosylation and Phosphorylation. *Circulation Research*, **93**, 1047-1058. https://doi.org/10.1161/01.res.0000103190.20260.37

[4] Decourcelle, A., Leprince, D. and Dehennaut, V. (2019) Regulation of Polycomb Repression by *O*-GlcNAcylation: Linking Nutrition to Epigenetic Reprogramming in Embryonic Development and Cancer. *Frontiers in Endocrinology*, **10**, Article 117. https://doi.org/10.3389/fendo.2019.00117

[5] Hart, G.W., Housley, M.P. and Slawson, C. (2007) Cycling of O-Linked *β-N*-Acetylglucosamine on Nucleocytoplasmic Proteins. *Nature*, **446**, 1017-1022. https://doi.org/10.1038/nature05815

[6] He, X., Hu, X., Wen, G., Wang, Z. and Lin, W. (2023) O-GlcNAcylation in Cancer Development and Immunotherapy. *Cancer Letters*, **566**, Article ID: 216258. https://doi.org/10.1016/j.canlet.2023.216258

[7] Xie, S., Jin, N., Gu, J., Shi, J., Sun, J., Chu, D., *et al*. (2016) O-GlcNAcylation of Protein Kinase a Catalytic Subunits Enhances Its Activity: A Mechanism Linked to Learning and Memory Deficits in Alzheimer's Disease. *Aging Cell*, **15**, 455-464. https://doi.org/10.1111/acel.12449

[8] Yang, W.H., Park, S.Y., Nam, H.W., Kim, D.H., Kang, J.G., Kang, E.S., *et al*. (2008) NF*κ*B Activation Is Associated with Its *O*-GlcNAcylation State under Hyperglycemic Conditions. *Proceedings of the National Academy of Sciences of the United States of America*, **105**, 17345-17350. https://doi.org/10.1073/pnas.0806198105

[9] Yuzwa, S.A., Shan, X., Macauley, M.S., Clark, T., Skorobogatko, Y., Vosseller, K., *et al*. (2012) Increasing *O*-GlcNAc Slows Neurodegeneration and Stabilizes Tau against Aggregation. *Nature Chemical Biology*, **8**, 393-399. https://doi.org/10.1038/nchembio.797

[10] Yuzwa, S.A. and Vocadlo, D.J. (2014) O-GlcNAc and Neurodegeneration: Biochemical Mechanisms and Potential Roles in Alzheimer's Disease and Beyond. *Chemical Society Reviews*, **43**, 6839-6858. https://doi.org/10.1039/c4cs00038b

[11] Zhang, C., Atasoy, D., Araç, D., Yang, X., Fucillo, M.V., Robison, A.J., *et al*. (2010) Neurexins Physically and Functionally Interact with GABAA Receptors. *Neuron*, **66**, 403-416. https://doi.org/10.1016/j.neuron.2010.04.008

[12] Zhang, Q., Lenardo, M.J. and Baltimore, D. (2017) 30 Years of NF-*κ*B: A Blossoming of Relevance to Human Pathobiology. *Cell*, **168**, 37-57. https://doi.org/10.1016/j.cell.2016.12.012

[13] Zhang, Z., Tan, E.P., VandenHull, N.J., Peterson, K.R. and Slawson, C. (2014) O-GlcNAcase Expression Is Sensitive to Changes in O-GlcNAc Homeostasis. *Frontiers in Endocrinology*, **5**, Article 206. https://doi.org/10.3389/fendo.2014.00206

[14] Zhu, Q., Cheng, X., Cheng, Y., Chen, J., Xu, H., Gao, Y., *et al*. (2020) O-GlcNAcylation Regulates the Methionine Cycle to Promote Pluripotency of Stem Cells. *Proceedings of the National Academy of Sciences of the United States of America*, **117**, 7755-7763. https://doi.org/10.1073/pnas.1915582117

[15] Zhu, Y., Wang, Y., Yao, R., Hao, T., Cao, J., Huang, H., *et al*. (2017) Enhanced Neuroinflammation Mediated by DNA Methylation of the Glucocorticoid Receptor Triggers Cognitive Dysfunction after Sevoflurane Anesthesia in Adult Rats Subjected to Maternal Separation during the Neonatal Period. *Journal of Neuroinflammation*, **14**, Article 6. https://doi.org/10.1186/s12974-016-0782-5

[16] Dong, X., Shu, L., Zhang, J., Yang, X., Cheng, X., Zhao, X., *et al*. (2023) Ogt-Mediated O-GlcNAcylation Inhibits Astrocytes Activation through Modulating NF-*κ*B Signaling Pathway. *Journal of Neuroinflammation*, **20**, Article No. 146. https://doi.org/10.1186/s12974-023-02824-8

[17] Zhang, D., Cai, Y., Chen, M., Gao, L., Shen, Y. and Huang, Z. (2015) Ogt-Mediated O-GlcNAcylation Promotes NF-*κ*B Activation and Inflammation in Acute Pancreatitis. *Inflammation Research*, **64**, 943-952. https://doi.org/10.1007/s00011-015-0877-y

[18] Yang, Y.R., Kim, D.H., Seo, Y., Park, D., Jang, H., Choi, S.Y., *et al*. (2015) Elevated O-GlcNAcylation Promotes Colonic Inflammation and Tumorigenesis by Modulating NF-*κ*B Signaling. *Oncotarget*, **6**, 12529-12542. https://doi.org/10.18632/oncotarget.3725

[19] Motolani, A., Martin, M., Wang, B., Jiang, G., Alipourgivi, F., Huang, X., *et al*. (2023) Critical Role of Novel O-GlcNAcylation of S550 and S551 on the P65 Subunit of NF-*κ*B in Pancreatic Cancer. *Cancers*, **15**, Article 4742. https://doi.org/10.3390/cancers15194742

[20] Dong, H., Liu, Z. and Wen, H. (2022) Protein O-GlcNAcylation Regulates Innate Immune Cell Function. *Frontiers in Immunology*, **13**, Article 805018. https://doi.org/10.3389/fimmu.2022.805018

[21] Ma, Z., Vocadlo, D.J. and Vosseller, K. (2013) Hyper-O-GlcNAcylation Is Anti-Apoptotic and Maintains Constitutive NF-*κ*B Activity in Pancreatic Cancer Cells. *Journal of Biological Chemistry*, **288**, 15121-15130. https://doi.org/10.1074/jbc.m113.470047

[22] Nakagawa, T., Furukawa, Y., Hayashi, T., Nomura, A., Yokoe, S., Moriwaki, K., *et al*. (2019) Augmented O-GlcNAcylation Attenuates Intermittent Hypoxia-Induced Cardiac Remodeling through the Suppression of NFAT and NF-*κ*B Activities in Mice. *Hypertension Research*, **42**, 1858-1871. https://doi.org/10.1038/s41440-019-0311-x

[23] Li, Y., Liu, H., Xu, Q., Du, Y. and Xu, J. (2014) Chitosan Oligosaccharides Block LPS-Induced O-GlcNAcylation of NF-*κ*B and Endothelial Inflammatory Response. *Carbohydrate Polymers*, **99**, 568-578. https://doi.org/10.1016/j.carbpol.2013.08.082

[24] Pellegrini, S. and Dusanter-Fourt, I. (1997) The Structure, Regulation and Function of the Janus Kinases (JAKs) and the Signal Transducers and Activators of Transcription (STATS). *European Journal of Biochemistry*, **248**, 615-633. https://doi.org/10.1111/j.1432-1033.1997.00615.x

[25] Liongue, C., O'Sullivan, L.A., Trengove, M.C. and Ward, A.C. (2012) Evolution of JAK-STAT Pathway Components: Mechanisms and Role in Immune System Development. *PLOS ONE*, **7**, e32777. https://doi.org/10.1371/journal.pone.0032777

[26] Du, X., Wang, B., Liu, X., Liu, X., He, Y., Zhang, Q., *et al*. (2017) Comparative Transcriptome Analysis of Ovary and Testis Reveals Potential Sex-Related Genes and Pathways in Spotted Knifejaw Oplegnathus Punctatus. *Gene*, **637**, 203-210. https://doi.org/10.1016/j.gene.2017.09.055

[27] Zhang, Z., Ma, P., Li, Q., Xiao, Q., Sun, H., Olasege, B.S., *et al*. (2018) Exploring the Genetic Correlation between Growth and Immunity Based on Summary Statistics of Genome-Wide Association Studies. *Frontiers in Genetics*, **9**, Article 393. https://doi.org/10.3389/fgene.2018.00393

[28] Auernhammer, C.J., Chesnokova, V., Bousquet, C. and Melmed, S. (1998) Pituitary Corticotroph SOCS-3: Novel Intracellular Regulation of Leukemia-Inhibitory Factor-Mediated Proopiomelanocortin Gene Expression and Adrenocorticotropin Secretion. *Molecular Endocrinology*, **12**, 954-961. https://doi.org/10.1210/mend.12.7.0140

[29] Herrera, S.C. and Bach, E.A. (2019) JAK/STAT Signaling in Stem Cells and Regeneration: From *Drosophila* to Vertebrates. *Development*, **146**, dev167643. https://doi.org/10.1242/dev.167643

[30] Kornfeld, J. (2008) The Different Functions of Stat5 and Chromatin Alteration through Stat5 Proteins. *Frontiers in Bioscience*, **13**, 6237-6254. https://doi.org/10.2741/3151

[31] Briscoe, J., Guschin, D. and Müller, M. (1994) Signal Transduction: Just Another Signalling Pathway. *Current Biology*, **4**, 1033-1035. https://doi.org/10.1016/s0960-9822(00)00236-0

[32] Images SSMAFM. https://smart.servier.com

[33] Bond, M.R. and Hanover, J.A. (2015) A Little Sugar Goes a Long Way: The Cell Biology of O-GlcNAc. *Journal of Cell Biology*, **208**, 869-880. https://doi.org/10.1083/jcb.201501101

[34] Love, D.C. and Hanover, J.A. (2005) The Hexosamine Signaling Pathway: Deciphering the "O-GlcNAc Code". *Science's STKE*, **2005**, re13. https://doi.org/10.1126/stke.3122005re13

[35] Krämer, O.H. and Moriggl, R. (2012) Acetylation and Sumoylation Control STAT5 Activation Antagonistically. *JAK-STAT*, **1**, 203-207. https://doi.org/10.4161/jkst.21232

[36] Liu, J., Qian, C. and Cao, X. (2016) Post-Translational Modification Control of Innate Immunity. *Immunity*, **45**, 15-30. https://doi.org/10.1016/j.immuni.2016.06.020

[37] Enchev, R.I., Schulman, B.A. and Peter, M. (2014) Protein Neddylation: Beyond Cullin-Ring Ligases. *Nature Reviews*

Molecular Cell Biology, **16**, 30-44. https://doi.org/10.1038/nrm3919

[38] Alleyn, M., Breitzig, M., Lockey, R. and Kolliputi, N. (2018) The Dawn of Succinylation: A Posttranslational Modification. *American Journal of Physiology-Cell Physiology*, **314**, C228-C232. https://doi.org/10.1152/ajpcell.00148.2017

[39] Van Nguyen, T., Angkasekwinai, P., Dou, H., Lin, F., Lu, L., Cheng, J., *et al*. (2012) Sumo-Specific Protease 1 Is Critical for Early Lymphoid Development through Regulation of STAT5 Activation. *Molecular Cell*, **45**, 210-221. https://doi.org/10.1016/j.molcel.2011.12.026

[40] Rani, A. and Murphy, J.J. (2016) STAT5 in Cancer and Immunity. *Journal of Interferon & Cytokine Research*, **36**, 226-237. https://doi.org/10.1089/jir.2015.0054

[41] Chen, P., Chi, J. and Boyce, M. (2018) Functional Crosstalk among Oxidative Stress and O-GlcNAc Signaling Pathways. *Glycobiology*, **28**, 556-564. https://doi.org/10.1093/glycob/cwy027

[42] Kang, J.G., Park, S.Y., Ji, S., Jang, I., Park, S., Kim, H.S., *et al*. (2009) O-GlcNAc Protein Modification in Cancer Cells Increases in Response to Glucose Deprivation through Glycogen Degradation. *Journal of Biological Chemistry*, **284**, 34777-34784. https://doi.org/10.1074/jbc.m109.026351

[43] Taylor, R.P., Geisler, T.S., Chambers, J.H. and McClain, D.A. (2009) Up-Regulation of O-GlcNAc Transferase with Glucose Deprivation in HepG2 Cells Is Mediated by Decreased Hexosamine Pathway Flux. *Journal of Biological Chemistry*, **284**, 3425-3432. https://doi.org/10.1074/jbc.m803198200

[44] Xiao, Z., Dai, Z. and Locasale, J.W. (2019) Metabolic Landscape of the Tumor Microenvironment at Single Cell Resolution. *Nature Communications*, **10**, Article No. 3763. https://doi.org/10.1038/s41467-019-11738-0

[45] Winkler, J., Abisoye-Ogunniyan, A., Metcalf, K.J. and Werb, Z. (2020) Concepts of Extracellular Matrix Remodelling in Tumour Progression and Metastasis. *Nature Communications*, **11**, Article No. 5120. https://doi.org/10.1038/s41467-020-18794-x

[46] Pan, D. and Jia, D. (2021) Application of Single-Cell Multi-Omics in Dissecting Cancer Cell Plasticity and Tumor Heterogeneity. *Frontiers in Molecular Biosciences*, **8**, Article 757024. https://doi.org/10.3389/fmolb.2021.757024

[47] Jiang, Y., Guo, H., Tong, T., Xie, F., Qin, X., Wang, X., *et al*. (2022) lncRNA Lnc-POP1-1 Upregulated by VN1R5 Promotes Cisplatin Resistance in Head and Neck Squamous Cell Carcinoma through Interaction with MCM5. *Molecular Therapy*, **30**, 448-467. https://doi.org/10.1016/j.ymthe.2021.06.006

[48] Su, Y., Wu, C., Chang, Y., Li, L., Chen, Y., Jia, X., *et al*. (2022) USP17L2-SIRT7 Axis Regulates DNA Damage Repair and Chemoresistance in Breast Cancer Cells. *Breast Cancer Research and Treatment*, **196**, 31-44. https://doi.org/10.1007/s10549-022-06711-3

[49] Kayagaki, N., Webster, J.D. and Newton, K. (2024) Control of Cell Death in Health and Disease. *Annual Review of Pathology: Mechanisms of Disease*, **19**, 157-180. https://doi.org/10.1146/annurev-pathmechdis-051022-014433

[50] Shi, L., Tang, X., Qian, M., Liu, Z., Meng, F., Fu, L., *et al*. (2018) A Sirt1-Centered Circuitry Regulates Breast Cancer Stemness and Metastasis. *Oncogene*, **37**, 6299-6315. https://doi.org/10.1038/s41388-018-0370-5

[51] Ferrer, C.M., Lu, T.Y., Bacigalupa, Z.A., Katsetos, C.D., Sinclair, D.A. and Reginato, M.J. (2016) O-glcNAcylation Regulates Breast Cancer Metastasis via SIRT1 Modulation of FOXM1 Pathway. *Oncogene*, **36**, 559-569. https://doi.org/10.1038/onc.2016.228

[52] Yan, W., Cao, M., Ruan, X., Jiang, L., Lee, S., Lemanek, A., *et al*. (2022) Cancer-Cell-Secreted miR-122 Suppresses O-GlcNAcylation to Promote Skeletal Muscle Proteolysis. *Nature Cell Biology*, **24**, 793-804. https://doi.org/10.1038/s41556-022-00893-0

[53] Yang, W.H., Kim, J.E., Nam, H.W., Ju, J.W., Kim, H.S., Kim, Y.S., *et al*. (2006) Modification of P53 with O-Linked N-Acetylglucosamine Regulates P53 Activity and Stability. *Nature Cell Biology*, **8**, 1074-1083. https://doi.org/10.1038/ncb1470