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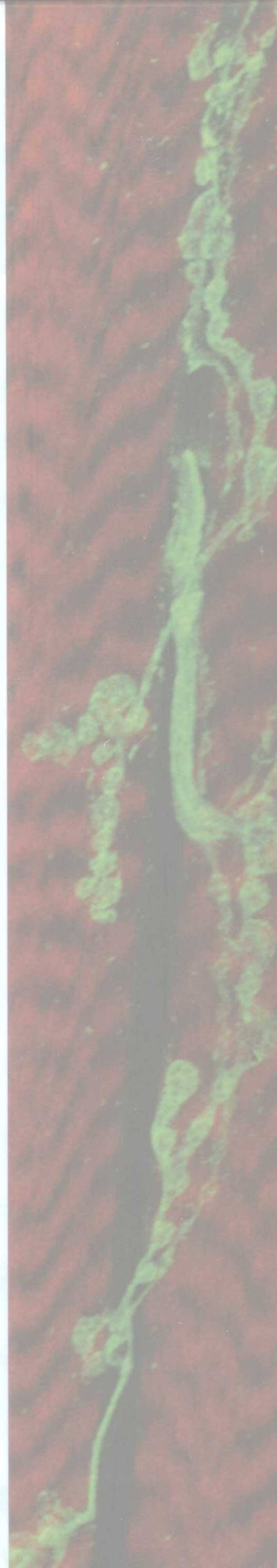
Handbook of Glycomics

糖组学手册

Richard D. Cummings and J. Michael Pierce



ELSEVIER
原版引进

科学出版社

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科 学 出 版 社

北 京

图字:01-2010-7409 号

This is an annotated version of
Handbook of Glycomics
Edited by Richard D. Cummings and J. Michael Pierce.

ISBN: 978-0-12-373600-0

图书在版编目(CIP)数据

糖组学手册 = Handbook of Glycomics:英文/(美)卡明斯(Cummings, R. D.)主编. —北京:科学出版社, 2011

ISBN 978-7-03-031120-7

Ⅰ. ①糖… Ⅱ. ①卡… Ⅲ. ①碳水化合物-手册-英文 Ⅳ. ①Q53-62

中国版本图书馆 CIP 数据核字(2011)第 101874 号

责任编辑:孙红梅　李小汀
责任印制:钱玉芬/封面设计:耕者设计工作室

科学出版社 出版
北京东黄城根北街 16 号
邮政编码:100717
http://www.sciencep.com

北京佳信达欣艺术印刷有限公司 印刷
科学出版社发行　各地新华书店经销

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2011 年 6 月第 一 版　开本:787×1092　1/16
2011 年 6 月第一次印刷　印张:31　插页:8
印数:1—1 800　字数:750 000

定价:128.00 元

(如有印装质量问题,我社负责调换)

一本系统理解前沿性糖组学研究的书

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近年来，糖复合物（Glycoconjugate）、糖链或聚糖（Glycan）、糖组学（Glycomics）、糖组（Glycome）等名词逐渐展现在生物学家面前。糖链或聚糖在传统的生物化学教科书中，泛指由葡萄糖等单糖聚合而成的物质，代表性的有淀粉、纤维素类的能量物质，也有人们经常听到的香菇聚糖等。但是，当前生物学家所关注的糖链主要是指与蛋白质、脂类等结合的，由10种单糖分子（葡萄糖、甘露糖、半乳糖、岩藻糖、唾液酸、N-乙酰葡萄糖胺、N-乙酰半乳糖胺、木糖、葡萄糖醛酸，以及艾杜糖醛酸等）组合而成的细胞结构物质，它与蛋白质、脂类分子共同形成了糖复合物。糖链及糖复合物参与了生命过程中胚胎发育、细胞分化、生殖、免疫、炎症、癌变及感染等所有的生理过程和病理过程，糖链已成为生命活动中极为重要的生物大分子物质。

提到生物信息，人们首先会想到核酸，包括脱氧核糖核酸（DNA）和核糖核酸（RNA）。依据生物的中心法则，生物信息流从DNA→RNA→蛋白质。核酸主要存在于细胞核内，DNA→RNA→蛋白质构成了细胞内的信息流，但是细胞与细胞间的信息交流离不开细胞表面及细胞分泌的物质分子。糖链主要存在于细胞表面的膜蛋白、糖脂和分泌蛋白上，糖链就像细胞的衣服包被在细胞的表面，构成了细胞的天线和触角。生物体功能的主要执行者为蛋白质，蛋白质的糖基化即糖链修饰是蛋白质翻译后的重要修饰之一，细胞50%以上的蛋白质具有糖链。因此，在以细胞为基础的生命舞台上，糖链扮演着不可或缺的生物信息分子的重要功能角色。

由于糖链结构的复杂性、不均一性及研究手段的匮乏，长期以来人们对其结构功能知之甚少，无法与核酸、蛋白质相比。糖生物学研究经历了一个艰辛发展的过程，正如本书作者所言，二十世纪的糖生物学家们如同在地狱中开展研究。直至二十世纪末，伴随着基因组学和蛋白质组学研究的深入，伴随着各种新生代的生物质谱技术，方兴未艾的化学生物学技术手段的涌现和发展，人们终于开始揭开糖链神秘的面纱。在二十一世纪初期，一门以研究糖复合物及其糖链结构功能为目标的糖组学研究学科诞生了，它综合系统地研究糖链的结构、糖链形成的分子机制、糖链的功能。糖组学研究与以往单糖和聚糖的生物学研究不同，它是一门新兴的结合了化学、生物学、生物化学、分子生物学、细胞生物学及临床医学等多学科的新型交叉学科。糖组学既包含各种新研究技术的开发，又包含各种学科的基础研究，是一项学科交叉高度信息集成的系统生物学研究。

由美国埃默里大学医学院教授Richard D. Cummings和美国佐治亚大学肿瘤研究中心和复合碳水化合物研究中心的J. Michael Pierce教授主编的《糖组学手册》，系统全面地介绍了糖组学的研究进展和概况。

该书从三类主要的糖复合物——糖蛋白、糖脂及糖胺聚糖出发，详细系统地介绍了糖链的分离、糖复合物的结构分析、糖链表达结构分析、糖链形成基因的表达、糖链与蛋白质的相互作用、糖链的数据信息库，以及各种模式动物物种的糖组学和疾病相关的

糖组学研究。该书共分六个章节，第一章概述了如何利用各种色谱技术与质谱技术分离纯化和分析鉴定蛋白质的 N-糖链、O-糖链和糖胺聚糖（蛋白聚糖）的结构。第二章旨在介绍糖链表达。其中，第一部分介绍了利用稳定同位素标记技术与质谱技术相结合，定量标记分析相同糖链结构的表达差异。第二部分先基础性地介绍了糖链的组成单元，蛋白质 N-糖链、O-糖链、糖脂糖链的生物合成过程，随后系统概述了合成糖链的糖基因（糖基转移酶）的研究技术和方法及相关的糖基因数据库，最后介绍了糖基因表达谱的研究手段，糖基因的转录表达数据与蛋白质数据和结构数据的相关研究，书中称其为糖的转录组学（Glycotranscriptomics）。第三章介绍了基于蛋白质与糖链相互作用的糖链芯片技术、凝集素结合色谱技术，以及蛋白质凝集素芯片技术的原理及其应用实例。第四章为糖生物信息学部分，介绍了糖组学技术所产生的大量信息数据的整合策略。系统介绍了日本的 KEGG 糖组学数据库和目前国际上通用的主要碳水化合物数据库，如 CCSD（CarbBank），BCSDB，CFG Glycan Database，以及欧洲的 EUROCarb DB。第五章针对不同的研究对象，介绍了糖组学在免疫系统细胞、人、鼠、果蝇、疟疾、血吸虫寄生虫病等方面的研究情况。阐述了各种模式生物的糖链的结构特征和功能。第六章系统介绍了疾病糖组学研究。读者从本章第一部分可以了解与肿瘤发生发展相关的糖蛋白质组学研究，作者介绍了从血清、组织、培养细胞等发现肿瘤标志物糖蛋白，以及糖链的研究策略。第二部分系统介绍了现已发现的因糖基因突变或缺失而导致的先天性糖基化紊乱引起的遗传性疾病。作者提出了如何通过糖组学与临床医学、遗传学相结合，利用各种模式动物，以糖链为靶标开发新的疾病诊断和治疗技术的策略，以及目前研究存在的挑战。

该书适用于对糖生物学研究内容感兴趣的所有读者，包括从事遗传学、蛋白质组学、系统生物学、生物信息学和临床医学的学生和研究人员。这是一本信息集成极高、专业性较强的糖生物学专业参考书，此书将帮助读者了解糖链研究的全貌。

糖链是神秘的，研究糖链需要勇气和毅力，二十一世纪的糖生物学家是快乐的。

张　延
写于二零一一年五月九日
上海交通大学系统生物医学研究院新楼启用满月纪念

前　　言

“甜蜜生活的体验。”

——引自但丁·阿利基埃里的《神曲》天堂部分，第二十章第 48 句

曾几何时，复杂的碳水化合物被众多科学家当作令人厌烦的物质，它的结构复杂到令人绝望，它的功能却鲜为人知。曾有观点认为细胞合成糖链（Glycan）是为了细胞的运动或者仅是一种细胞的“装饰”，而并非其功能的需要；还有观点认为不同细胞间糖链结构上的差异可能是一种随机的表面变化现象，而非遗传控制所致。那些身处二十世纪后期的糖科学家们，在研究糖链时仿佛但丁在地狱中所描述的那样，他们发现自己陷入了无法理解糖链结构与功能的泥潭中，他们深刻领悟到了地狱之门的告诫：“所有进去的人啊，放弃希望吧。”

然而，随着从酵母到人的全基因组中具有开放阅读框（ORF）的基因数量的确定，现在已无人质疑，细胞所制造的每一个蛋白或任何产物（这里指糖链）具有特定的功能，尤其是那些通过同一途径上的多个蛋白共同作用而产生的糖链。因此，新时代带来了新的认识，今天的糖科学研究者们不再于地狱中苦苦挣扎，而是开始升入但丁诗中的天堂，成为受膏者。

近年所发现的一系列糖链的重要功能给人留下了深刻的印象：

- 糖基化参与溶酶体酶生物合成的调节和靶向分子的糖基化作用。
- 糖链调控初期炎症免疫应答现象，如白血球的黏附和翻转、淋巴细胞的归巢。
- 糖链参与介导多种病原体的识别和感染，包括与树突状细胞凝集素结合的 HIV 病毒的感染。
- 糖基转移酶基因的突变和缺失导致出生缺陷型先天糖基化紊乱综合征。
- 糖基转移酶变异导致“肌-眼-脑病”类肌肉营养不良家族遗传病的发生。
- 蛋白质丝氨酸或苏氨酸上的 O-GlcNAc（N-乙酰葡萄糖胺）修饰参与各类转录因子及胰岛素抵抗等信号通路的调控。
- 蛋白质的 N-糖基化修饰参与内质网、高尔基体中蛋白质生物合成的质量控制。
- 硫酸肝素类糖胺聚糖在细胞信号转导、血管新生及血液凝固中的重要作用。
- 糖链被各种免疫细胞（如巨噬细胞和树突状细胞）表面抗原识别，糖链与糖结合蛋白的相互作用调节免疫细胞的免疫应答。
- 唾液酸结合蛋白控制粒性白细胞的分化。

因为新的糖链功能被不断地发现，整个糖科学研究领域的发展让人感到无比振奋、充满了期望。

所有的生命现象均受控于特定的糖链结构。这些特定的糖链结构既受生物合成的调

控，又被特有的糖结合蛋白或凝集素所识别。二十一世纪初具有显著标志的科学进展是蛋白质翻译后修饰分析技术和分析方法的进步，特别是糖链结构分析技术的进步为加速理解和发现糖链的功能奠定了基础。研究手段和技术的进步孕育了建立在生物学和生物化学研究基础上的糖组学（Glycomics）的诞生。作为二十一世纪重要研究领域之一的糖组学，其目标是确定人和动物的全糖组（Glycom）。本书中定义的“糖组学”所涉及的范围很广，包含所有与糖链相关的分子，即包括糖链分子本身及那些调控糖链结构合成或被糖链调控的所有分子。因此，糖组学研究充满了挑战，我们既要理解和揭示糖链的结构、被糖链修饰的各类分子，还要确定在疾病及生长发育过程中，不同细胞上糖链的表达变化。

《糖组学手册》介绍了当今糖组学研究最新的技术手段，以及它们在揭示糖组数量变化及其在特定器官、细胞和疾病研究中的应用。为了更全面地理解本书所涉及的糖生物学和糖科学的基础知识，读者可以参考 2009 年冷泉港实验室出版社出版的《糖生物学基础》（第二版）。

参与编写《糖组学手册》的作者都是长期从事各种糖复合物研究的专家，他们在利用各种新方法研究不同糖复合物的糖链结构中积累了丰富的经验。这些糖复合物包括糖蛋白、糖脂和糖胺聚糖。作者们把糖链结构、基因表达和糖生物信息学的知识整合到一个系统性研究的层面，通过整体阐述来帮助我们更完整地理解糖链在生理发育和疾病发展过程中的作用。本书由六个章节组成。第一章为糖复合物结构分析，在本章中 Meschref 和 Novotny 介绍了 N-聚糖的分析；Wells 介绍了 O-聚糖的组成及糖蛋白质组学的分析手段；Zhang，Zhang 和 Linhardt 描述了复杂天然糖胺聚糖的分析。第二章为糖链的表达转录组（Glycotranscriptomics）技术，该章中 Cummings 和 Smith 综述了与稳定同位素标记相结合的质谱方法在各种不同来源的糖链结构定量差异分析中的应用；然后，Nairn 和 Moremen 介绍了糖的转录组研究技术，即研究调控糖组合成和糖组识别的糖基因表达。第三章为蛋白质-糖链相互作用，Smith 和 Cummings 总结了糖链芯片在糖结合蛋白和凝集素识别中的应用；Hirabayashi 介绍了色谱和质谱技术是如何用于定义糖和蛋白的相互作用。第四章，糖生物信息学：包括 York，Kochut 和 Miller 编写的有关整合糖组学信息和数据库的内容，Hashimoto 和 Kanehisa 介绍了 KEGG 分析网站在糖组学中的进展，它是如何整合糖链的生物合成途径信息、基因信息和糖链结构信息；Ranzinger，Herget，Lütteke 和 Frank 介绍了用同一数据语言来描述和整合不同来源的糖链相关数据的欧洲糖组数据库（EUROCarb DB）。第五章概述了不同物种的全糖组，Redelinghuys 和 Crocker 介绍了免疫系统的功能全糖组；North，Chalabi，Sutton-Smith，Dell 和 Haslam 介绍了人和小鼠的全糖组研究；Sharrow，Aoki，Baas，Porterfield 和 Tiemeyer 介绍了果蝇的全糖组研究，Davidson 介绍了关于疟疾的研究，van Die 和 Cummings 介绍了关于寄生虫的研究。第六章讨论了疾病糖组，Pierce 讨论了癌症糖组学，Freeze 和 Eklund 则讨论了糖链与人的糖基化紊乱症。

《糖组学手册》是一本广泛理解糖组学研究内容的入门手册，正是因为糖组、糖结合蛋白、酶（糖基转移酶和糖苷酶），以及它们在微生物、寄生虫、植物、动物研究中新信息的不断涌现，糖组学研究内容得到了极大的丰富和发展。糖组学的多样性研究构成了本书的亮点。对现有技术和概念的总结无疑让本手册成为一本在未来几年内都颇有

价值的参考书，它将帮助感兴趣的读者从深度和多样性上进一步理解这个快速发展并且令人激动的生物大分子物质——糖链。

在此，向帮助促成本书出版的人们表示诚挚的感谢，包括众多慷慨地回应和协助我们的撰稿人，以及 Elsevier 出版集团优秀的工作人员，尤其是组稿编辑 Christine Masahina 和管理编辑 Rogue Schindler。

“我们可以拥有的最美丽的经验就是神秘的事物。”

——阿尔伯特·爱因斯坦

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（张延　译）

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Preface

"L'esperienza de questa dolce vita."
The experience of this sweet life.

Dante Alighieri, *La Divina Commedia, Paradiso*, Canto XIX

Many of us remember when complex carbohydrates were viewed by most scientists simply as nuisances whose structures were hopelessly complicated and whose functions at best were obscure. Arguments were made that cells synthesized their glycans more for sport or even "decoration" than for necessity, and that differences in glycan structures between cells might be epigenetic irrelevancies, rather than genetically controlled essentials. If Dante had been a scientist in the latter part of the twentieth century, he surely would have assigned a level in his *Inferno* to those who found themselves mired in understanding glycan structure and function, and who understood well the warning at *Inferno's* entrance, "Abandon hope all ye who enter." With the shrinking number of open reading frames (ORFs) identifiable in genomes from humans to yeast, however, no one would now hypothesize that a cell makes a protein or any product, especially those made by the action of several proteins within a pathway, which serves no particular function. Thus, with new times comes new knowledge; surely now Dante would have the glycoscientists ascend to *Paradiso* to join the anointed ones.

The list of recent discoveries showing critical functions of glycans is impressive:

- Regulation of lysosomal enzyme biosynthesis and the roles of glycosylation in molecular targeting
- Regulation of the initial steps of the inflammatory response and leukocyte adhesion and turnover, as well as lymphocyte homing
- Mediation of the recognition and infection by many pathogens, including HIV, via dendritic cell lectins
- Identification of the family of congenital disorders of glycosylation that cause birth defects
- Demonstration that mutations in glycosyltransferases cause a form of muscular dystrophy known as the muscle–eye–brain disease
- A Ser/Thr modification by *N*-acetylglucosamine, O-linked GlcNAc, serves to regulate diverse signaling pathways, from transcription factor binding to insulin resistance
- Understanding that protein *N*-glycosylation fundamentally controls glycoprotein quality control and biosynthesis in the endoplasmic reticulum/Golgi apparatus
- Multiple activities of glycosaminoglycans, including heparan sulfate, regulate cell signaling and angiogenesis, as well as blood clotting

- Glycans are recognized by antigen-presenting cells, including macrophages and dendritic cells, via numerous glycan-binding proteins that regulate immune responses
- Sialic acid-binding proteins in leukocytes control cellular differentiation.

Moreover, throughout the field of glycoscience there is excitement and anticipation because new glycan functions are constantly being discovered.

All of these biological processes are controlled by specific glycan structures that are biosynthetically regulated and that are often recognized by specific glycan-binding proteins or lectins. A scientific hallmark of the first part of the twenty-first century, therefore, has been the development of technologies and methodologies to identify the details of post-translational modifications, in particular glycan structures, thus accelerating the pace of discovery of glycan function. These accomplishments have led to the establishment of glycomics as one of the fundamental areas of biological and biochemical study, and the ambitious goal of defining human and animal glycomes as one of the twenty-first century's most important quests. The definition of glycomics used in this book is very broad, encompassing all those molecules that contain glycans and which regulate or whose structure and function are regulated by glycans. Thus, this quest to understand the glycome is extraordinarily challenging, since it requires an understanding of both glycan structures and the molecules to which glycans are linked, and requires defining their altered expression in different cells during development and disease.

The *Handbook of Glycomics* contains descriptions of state-of-the-art technologies that are in current use to describe and quantify changes in glycomes, as well as the application of these technologies to the study of specific organisms, cells, and diseases. For a comprehensive background on glycobiology and glycoscience, readers are referred to the *Essentials of Glycobiology*, 2nd edition, 2009, Cold Spring Harbor Press.

The chapters in the *Handbook of Glycomics* were written by experts in the field with experience in studying glycan structures using newly developed methods for the analysis of many different types of glycoconjugates, including glycoproteins, glycolipids, and glycosaminoglycans/proteoglycans. Moreover, these authors are involved in integrating this knowledge into a systems approach to the field, incorporating glycan structure, gene expression, and glycobioinformatics to propel our understanding of the functions of glycans in physiology, development, and disease. The book is organized into six sections. In Section I, Glycoconjugate Structural Analysis, Meschref and Novotny describe *N*-glycan analysis and Wells describes O-glycan analysis using a glycoproteomics approach. The complex nature of glycosaminoglycan structural analysis is addressed by Zhang, Zhang, and Linhardt. In Section II on Glycotranscriptomics, the use of isotope labeling approaches to aid in mass spectrometry of glycans and the rapid identification of structural differences of glycans compared between different sources are described by Cummings and Smith. Then Nairn and Moremen describe the approaches used to analyze transcription of genes that regulate and recognize the glycomes. In Section III, Protein–Glycan Interactions, Smith and Cummings describe the use of glycan microarrays to identify glycan recognition by glycan-binding proteins and lectins, and Hirabayashi describes how chromatographic and mass spectrometric techniques are used to define glycan–protein interactions. Section IV, Glycobioinformatics, includes chapters by York, Kochut, and Miller on integrating glycomic information and databases, and by Hashimoto and Kanehisa on the development and use of the KEGG GLYCAN for integrating biosynthetic pathways, genetics, and glycan structures. Ranzinger, Herget, Lütteke, and Frank describe the European Glycomics Portal, which promotes integration of glycan-related data from many sources. Section V gives overviews of different glycomes and their relationships to functional glycomics and immunity, as described by Redelinghuys and Crocker in relation to the mouse and human immune systems; North, Chalabi, Sutton-Smith, Dell, and Haslam in regard to humans and mice; Sharrow, Aoki, Baas, Porterfield, and Tiemeyer in *Drosophila*; Davidson in malaria;

and van Die and Cummings in parasitic worms. The final section of the book, Section VI, is on Disease Glycomics, where cancer glycomics is discussed by Pierce, and glycans in human disorders of glycosylation are discussed by Freeze and Eklund.

The *Handbook of Glycomics* serves as a portal to these broad subjects on glycomics, since the field is expanding at a stunning pace, with information pouring in daily on glycomes, glycan-binding proteins, enzymes (glycosyltransferases and glycosidases), and transporters in microbes, parasites, plants, and animals. There are clearly many areas of research on glycomics that will need to be included in updated editions of the *Handbook*. The techniques and conceptual approaches described in this edition of the *Handbook of Glycomics* will no doubt be a valuable reference in this field for years to come, and will provide the interested reader both depth and diversity in this rapidly expanding and exciting component of biology.

We are indebted to those who have helped make this book possible, including the many authors who graciously responded to our requests and cajoling, along with the expert staff at Elsevier, including acquisitions editor Christine Masahina and developmental editor Rogue Schindler.

The most beautiful experience we can have is the mysterious.

—Albert Einstein

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Acknowledgments

The glycan analyses were performed by the Analytical Glycotechnology Core of the Consortium for Functional Glycomics (GM62116). Anne Dell was a Biotechnology and Biological Sciences Research Council (BBSRC) Professorial Fellow. We also acknowledge the efforts of various personnel from the CFG Mouse Transgenic Core F and M-Scan INC, 606, Brandywine Parkway, West Chester, PA 19380 USA. We also wish to acknowledge the efforts of Lisa Stocks, Executive Director of Lifesharing, the organ procurement organization of San Diego and her professional staff that undertook the collection and initial processing of the human tissue samples for this research.

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（张延　译）

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