



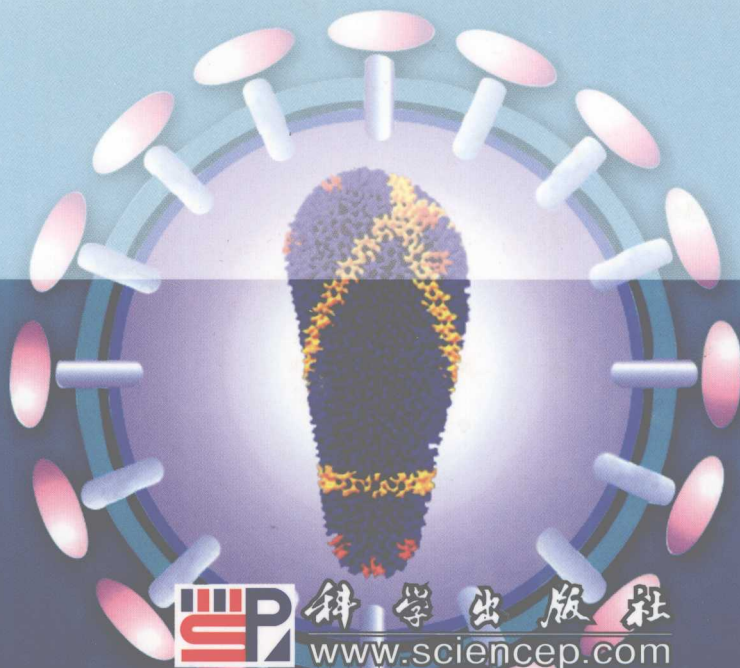
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HIV-1: Molecular Biology and Pathogenesis
Viral Mechanisms

HIV-1: 分子生物学和发病学 病毒机制 (第二版)

〔美〕蒋观德 (Kuan-Teh Jeang)



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HIV-1: MOLECULAR BIOLOGY AND PATHOGENESIS

Viral Mechanisms

Second Edition

HIV-1: 分子生物学和发病学

病毒机制

(第二版)

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Kuan-Teh Jeang

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导 读

人类免疫缺陷病毒(HIV)可以说是 20 世纪以来人类研究得最为广泛和深入的病毒之一。自 1981 年美国发现首例艾滋病患者起至今的 20 多年中,全球的顶尖科学家们在 HIV 分子病毒学、发病学、流行病学、免疫学、药物学和临床医学等领域开展了大量研究,并取得了一系列重要突破,其中最具影响力的成果包括:明确了艾滋病(AIDS)由 HIV 感染造成,明确鉴定 CD4、CCR5 和 CXCR4 是 HIV 的细胞受体,建立了高效抗逆转录病毒疗法(HAART)等。但 HIV 感染的原因和 AIDS 的发病机制仍旧十分含糊。这可能是人们在临床彻底治疗 AIDS 和 HIV 疫苗研制上接连不断遭遇失败的关键原因之一。而深入理解 HIV 与宿主之间的相互作用是寻获答案的唯一方式。近年的研究结果已经开始揭示隐藏于这些问题之下的分子细节。

这本《HIV-1:分子生物学和发病学:病毒机制》(第二版),是 Elsevier 出版社的系列丛书“药理学进展”(Advances in Pharmacology)中的第 55 辑,由美国国家卫生研究院(NIH)分子病毒研究室主任、知名华裔病毒学家蒋观德(Kuan-Teh Jeang)博士主编。

蒋观德博士 1984 年于美国约翰·霍普金斯大学(Johns Hopkins University)获医学博士学位,随后进入美国国家卫生研究院从事病毒学研究。蒋博士学术造诣深厚,成就显著:在潜心研究分子病毒的 20 多年间,他共获得了 6 个专业学术奖和 2 项专利,并在国际学术刊物上发表了 200 多篇文章,为艾滋病基础研究特别是病毒学研究领域做出了杰出贡献。

2000 年,蒋博士邀请来自北美、欧洲、澳大利亚和亚洲的 26 组著名艾滋病专家针对当下 HIV-1 研究现状撰写专题综述,并相继按类别分为“病毒机制”和“临床应用”两部专著结集出版,即“药理学进展”系列第 48 辑《HIV-1:分子生物学和发病学:病毒机制》(第一版)和第 49 辑《HIV-1:分子生物学和发病学:临床应用》(第一版)。近几年来,大量新的艾滋病研究成果不断涌现。2007 年,为更新艾滋病研究最新成果及记录面临的挑战,蒋观德博士再次联手多位国际知名艾滋病学术带头人,编撰第二版《HIV-1:分子生物学和发病学:病毒机制》,并邀请了艾滋病病毒的发现者之一,著名科学家 R. C. Gallo 为本书作序。

内容上看,本书共安排了 13 章,从分子生物学角度探讨 HIV-1 的生命周期,并对相关基因、蛋白分子结构和作用机制的基础研究进展进行了详细的综述。具体内容可归纳为四部分:

第一部分:病毒的入侵(第 2 章)

本章的主要着眼点在 HIV-1 的 Env 蛋白。HIV-1 的 Env 蛋白由病毒的 *env* 基因所编码,主要包括外膜蛋白 gp120 及跨膜蛋白 gp41。HIV-1 Env 蛋白在病毒的感染、侵入和干扰机体免疫功能等方面发挥着重要作用。本文通过描述 Env 蛋白与 CD4、复合受体、中和抗体之间的相互作用,论述了 Env 蛋白结构与功能研究的最新进展,并深入探讨了可用于设计疫苗免疫原和开发阻断 HIV 进入靶细胞候选药物的 Env 蛋白的结构要素。

第二部分:逆转录(第 3 章)

HIV-1 病毒侵入受体细胞后,就进入逆转录阶段。病毒 RNA 在逆转录酶(RT)的催化下,先形成线状的双链 DNA,而后环化成闭合的双链 DNA,后者被转运到细胞核,整合到细

胞染色体中。许多年前,人们曾试图通过改变 HIV-1 的 PBS(Primer binding site,即和 tRNA 的 3' 末端互补的一个 18 核苷酸序列)结构,来诱使 HIV-1 与非自身 tRNA 引物结合,但之前的尝试遇到了失败。近期一些病毒 RNA 与细胞 RNA 之间联系的新发现使得本章的作者,来自荷兰阿姆斯特丹大学的研究者们再度尝试改变 HIV-1 引物的特异性,他们在本章深入探讨了 PAS(Primer activation signal,引物激活信号)的识别与作用。

第三部分:基因表达与调控(第 4、5、6、7、11 章)

HIV-1 RNA 约由 9200 个碱基组成,其中含有 gag、env 和 pol 三种结构蛋白的基因以及 6 种调控基因(*Tat*, *Vif*, *Vpr*, *Vpu*, *Nef*, *Rev*)。调控基因编码辅助蛋白,调节病毒蛋白合成和复制。*Tat* 等 6 个基因分别表达 6 种蛋白质,对病毒复制起调控作用。第三部分内容分章节详细介绍了 HIV-1 调控基因和辅助蛋白的结构与功能。

第四部分:病毒包装与成熟(第 1、8、9、10 章)

当 HIV-1 在细胞内经过整合、表达和翻译之后,新合成的 HIV-1 病毒的壳体蛋白、酶与 RNA 在宿主细胞膜的内壁处聚集,病毒外膜蛋白也在细胞膜内聚集。尚未成熟的病毒颗粒从宿主细胞上以出芽的方式离开细胞,然后病毒中的蛋白酶将长链的蛋白质分子分割成小的病毒蛋白和酶,病毒才具有了感染能力。该部分章节系统分述了 HIV-1 的组装与成熟过程,其中着重探讨了可用于研发 AIDS 药物的蛋白质和酶的结构、功能及作用靶点。

此外,本书最后两章(第 12、13 章)还就病毒的致病性与治疗的关系进行了深入阐述。

第 12 章是关于 HIV-1 潜伏池的综述,HIV-1 的潜伏是清除患者体内 HIV-1 的最大障碍。只有完全了解 HIV-1 的潜伏机制,才可能彻底治疗 AIDS。

第 13 章是关于一项较新的研究成果的综述——RNA 干扰(RNA interference,或 RNAi)及其在抑制 HIV-1 感染中的作用。本章由本书的编者蒋观德博士与其科研团队的成员共同撰写。RNA 干扰现象是生物界近 10 年来最令人兴奋的发现之一,是分子生物学中最有力且必不可少的工具。它是指一种序列特异性的、转录后基因沉默(post-transcriptional gene silencing, PTGS)的过程,可以导致细胞和病毒的 RNA 降解。蒋博士和他的同事们在本章中报告了他们最近在解析 siRNA 及 miRNA(微型 RNA)与 HIV-1 病毒相互关系中所取得的新成果。然而,尽管 siRNA 及 miRNA 在研制 AIDS 新疗法等方面具有很大潜力,这项新研究仍然存在着许多具体操作上的问题。比如,很多 siRNA 与其在生物体系中靶标的关系和作用是否专一等问题,有待进一步深入研究和阐明。

至于上述基础研究进展如何影响艾滋病药物治疗、临床应用等方面,则由本书的姐妹篇,“药理学进展”第 56 辑——《HIV-1:分子生物学和发病学:临床应用》(第二版)进行探讨。

综合来看,《HIV-1:分子生物学和发病学:病毒机制》(第二版)是全面和系统反映当前国际 HIV 分子生物学研究进展的一本权威科学专著。本书及其姐妹篇可供高等院校和研究院所的研究生、博士后,从事 HIV 病毒学、药理学的高级研究人员和传染病临床医务工作者进行研究和参考。

杨荣阁

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前 言

数月前我身在欧洲,观看了 CNN 电视台反复播放的一个关于 HIV/AIDS 的节目。虽说总体来看,这个节目对加强 AIDS 防治意识,帮助宣传疫情状态、HIV 传播风险以及 HIV 治疗等方面的正确信息起到了非常积极的作用,但当我看到该节目的广告经常宣称本“秀”是由一群与观众平等互动的 HIV/AIDS 专家组成,我还是觉得受到了打击。据我所知,这群所谓的专家里没有一个是科学家。在这个节目的尾声,一位嘉宾,某影视明星,宣称人们的团结将会解决 HIV/AIDS 问题(或大体类似的说法)——但这不是科学事实。也许是我错了,但是他的言论不仅听起来太“政治正确”,太职业性团结,或诸如此类;这些言论还远离了科学,偏离了对事件真实发生过程的理解,这些都让人不寒而栗。

我忧心忡忡。随着科技发展的速度越来越快,科学本身、技术文明与群众之间出现了极大的代沟,甚至还出现了反科学的言论及敌视态度。正如他人提过的,200 多年前的受教育者,象本杰明·富兰克林和托马斯·杰佛逊,可以将严肃科学或发明创造当作是业余爱好,而且当时大部分人都能够理解他们。想想这对当今的政治人物和大多数社会人士来说是多么遥远的一件事。我们是否在教育社会大众中尽了足够的努力?我们能否做得更好,还是说仅仅因为如今做到这些太复杂太专业?我并没有答案,但是这些问题促人深思,也促使我们尽力改善科学家与普通大众间的交流。

回想那位影星的评论,回到本书的议题,难道我们不该至少去尝试认识一点:不是 50%、70%或 90%,而是实实在在 100%的 HIV/AIDS 在基础、概念以及实践上(包括诊断、预后和治疗)的研究进展均来自于基础科学,准确地说是来自于 HIV 分子生物学和发病学?也许我们可以举出三个例外:①早期(1981~1982)流行病学研究(主要由 James Curran 和他的同事完成)定义了危险人群及疾病的传播模式;②临床医生给了我们关键的信息,即存在着 $CD4^+$ T 细胞的显著减少;还有③ HIV 的早期分离与发现。然而,即便是在这三个公认例外的后两者中,我们也必须认识到基础科学(虽然不是 HIV 分子生物学或发病学)所扮演的角色。毕竟,CD4 的检测需要早期使用单克隆抗体发现这一细胞表面分子;HIV 的分离首先需要找到逆转录病毒的替代标记物,即对逆转录酶(reverse retrovirus)以及白细胞介素-2(IL-2)刺激原发性 T 细胞(primary T cells)增殖的精确检测。当然,逆转录酶(1970)和白细胞介素-2(1976)均来自基础研究。

无需在此详述其后产生巨大影响的研究进展,如 HIV 与 AIDS 的关系(因果)、HIV 血液检查的研究进展以及有效抗 HIV 治疗的发展,这些都完全来自 HIV 分子生物学/免疫学的基础研究:① HIV 检测中,培养 HIV 的永久细胞系是产生足量 HIV 蛋白的前提条件;②酶联免疫吸附试验(ELISA),特别是免疫印迹(Western Blot)——首次从基础研究应用于血液检测的确认实验(confirmatory blood test);③细胞系即便不是药物筛选所必需的,也被证明十分有价值,比如 AZT。我们还可以在治疗中加上逆转录酶和蛋白酶抑制剂,它们显然也是从早期分子生物学研究中得来的——先是动物逆转录病毒,然后是 HTLV-1 和 HTLV-2,最后是 HIV。谈到今后的治疗,我们都知道整合酶(targeting integrase)和膜融合抑制剂(原文 blocking HIV entry,在此译为膜融合抑制剂——译者注)即将或已经出现。当然,这些治疗途径完全依赖于分子生物学研究中,对 HIV 前病毒的整

合(前者)及 HIV 进入细胞步骤(后者)的充分认识。

我们也可以设想,将来的治疗可能会从 HIV 感染者的慢性免疫活化状态(chronic activation state)入手,而我们对于 HIV 感染进程中活化重要性的认识也直接来自于对 HIV/SIV 发病学的研究。

我们已认识到个体感染的 HIV 种类可能“实际上”很重要——在 Essex 及其同事们在西非进行的血清流行病学调查中,一个显著不同的 HIV 类型(HIV-2)终于得以定义,而我们都知悉它的致病力和感染力要小得多。大范围 HIV 毒株的分子生物学分析帮助定义了流行病学的趋势,帮助归类了治疗敏感性的不同、致病性的细微差别以及不同类型对疫苗反应的差别。最后,所有目前研制出的疫苗都至少是部分以 HIV 分子生物学为基础的。

本书这样的读物正是我们所需要的,但是我们也应该试着向更大范围的读者群提供通俗易懂的总结,希望出版商和编辑能够赞同这一点。

Robert C. Gallo

(杨荣阁 译)

“This book is dedicated by Kuan-Teh Jeang to Diane,
David, John and Diana Jeang.”

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Preface

Some months ago while in Europe, I saw a presentation on HIV/AIDS that was repeatedly shown on CNN. While overall it served a very positive function in that it enhanced awareness of the problem and helped disseminate correct information on the status of the epidemic, the risks of HIV transmission, and some aspects of HIV therapy, I was nonetheless struck by the oft-stated advertisement that the “show” was composed of HIV/AIDS experts handling a give and take with members of the audience. Yet, to my knowledge not even one member of the group of experts was a scientist. At the closure of this program, one panelist, a movie star, stated that HIV/AIDS would be solved by people coming together (or something close to this comment), and that it was not the science. I may be completely wrong, but his words sounded so “politically correct,” pro-“solidarity,” and all such things (whatever they mean), and at least so minimally near to science and to an understanding of how progress really occurs, that it gave me chills.

I am worried. As science and technology progress faster and faster, we have developed an enormous gap between science and our technical culture and the population at large, perhaps even to the point of occasional anti-science and hostility. As others have noted, it has been a little over 200 years since educated people such as Benjamin Franklin and Thomas Jefferson could do serious science and/or inventions as a hobby. A major portion of the population could understand them. Consider how remote that is today for a politician and for the mass of society. Are we doing enough to educate a broader mass of society? Can we do much better or is it now simply too complex and specialized? I do not know the answers, but it is a cause for pondering and for trying to improve our communications.

Going back to the remarks of the movie star and considering the topic of this book, should not we at least try to make it abundantly clear that not 50%, 70%, or 90%, but virtually 100% of *all* fundamental, conceptual, and *practical* (including diagnosis, prognosis, and therapy) advances in