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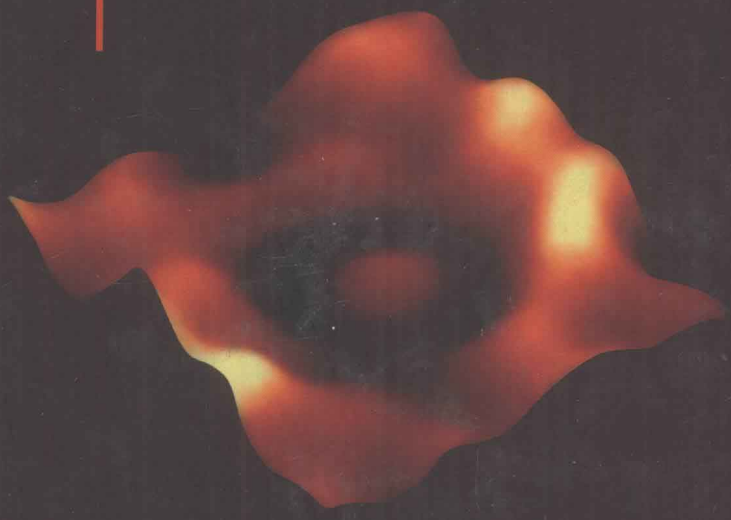
Methods in Nano Cell Biology

纳米细胞生物学方法

Bhanu P. Jena



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导　读

生命科学和纳米科学与技术在二十世纪中晚期均取得了长足的进展，而这种快速发展的趋势一直延续到今天，丝毫没有放缓脚步的迹象。当然，人类为满足自身发展需求而探索赖以存在的物质世界无疑是科技发展的最根本的推动力。这种略显“原始”的需求或明显或隐晦，但都存在于自古及今的各种发明创造之中。比如，计算机中央处理器之于纳米制造；人类健康需求之于生物医药，等等。从这个角度讲，人类每一次有目的的科学探索和重大科学工程的启动，都在不同程度上推动了相关学科的发展乃至催生了新的学科。而纳米科技和生命科学的产生与发展也同样建立在人类自身发展的需求上。从学科发展的角度看，虽然不同学科经过短则十几年长至几个世纪的发展，已经形成自身独特的视角和相对明确的研究范畴，但在特定的问题和领域，彼此间存在广泛交集。也可谓“君在长江头，我在长江尾”，却是“共饮长江水”的。也由此在不同的历史时期产生了许多所谓“交叉学科”。纳米科技和生命科学无疑带有浓重的交叉学科特色，不仅涉及物理、化学、数学等基本学科，同时与计算机科学、材料科学以及工程学等诸多领域相关。所以，纳米科技与生命科学的快速发展也应与其多学科交叉研究特点有关系。需要指出的是，纳米科技与生命科学彼此间的相互渗透与融合，同样产生了诸如纳米医学、纳米生物学、纳米生物技术等新兴学科，其发展引人瞩目并可寄予厚望。

对“纳米-生命”交叉科学感兴趣的读者而言，阅读由 Bhanu P. Jena 教授编纂的这本《纳米细胞生物学方法》专辑无疑是大有裨益的。如编者在前言中所讲，对于细胞生物学，“the ultimate goal，…is the understanding of cellular structure-function at atomic resolution and in real time in living cells”，而纳米科技的介入可以帮助我们进一步逼近这一宏伟目标。因此，该书选择性汇集了具有明显交叉学科特色的研究事例，并由科研一线的人员撰写，以展现纳米细胞生物学研究的现状和发展脉络，其中也不乏对未来发展的真知灼见。从内容上看，具有纳米分辨水平（空间分辨）的活细胞（生命本征）结构与功能的实时（时间分辨）研究成为贯穿各章节内容的主线，如原子力显微镜技术在活细胞分子行为研究中的应用，以及活细胞中蛋白质折叠、装配与解离过程研究，等等。另外，针对每种技术或方法，作者都给出了或详细或简略的背景资料及发展沿革，而研究内容则指向该领域的前沿，甚或提供了详尽的研究方案，因此该书不仅适合本领域专业人员，也同样有助于非本领域人员，如教学人员、研究生和高年级学生加深对这一新兴领域的认识。

“什么是纳米细胞生物学与技术?”，相信这一问题不止笔者关注，也是领域内外许多有兴趣的读者的问题。我们不妨回顾“纳米”的本征含义，即十亿分之一米。由于纳米尺度（～0.2～100nm）的物质开始受控于量子效应和表面效应，因此，纳米科技定位于阐明这些效应及其对物质特性的影响，并探索这些效应所产生的功能结构与系统。目前，没有证据显示生物分子可以表现出赖于纳米尺度的光、电、磁特性，但毋庸置疑，最高级的纳米尺度机器非生物系统的调控分子莫属，比如本书所例举的负责细胞分

泌的分子机器——“孔体”等。因此，从细胞研究角度讲，探索纳米尺度的分子机器的结构、装配、解离、运动、功能等，至少在目前构成了纳米细胞生物学的基本研究范畴。另外，在高度“拥挤”、结构复杂的细胞中，分子机器的动力学研究同样值得期待。由此也可大致勾勒出纳米细胞生物学的研究特点：具有生命本征性质，即建立活细胞中结构与功能的研究；具有纳米及亚纳米尺度的空间分辨能力；以及适当的时间分辨能力，即强调生物过程的实时研究。这也是该书内容所竭力推崇的。

从学科发展角度看，虽然纳米生物细胞学研究发展迅速，但仍处于起步阶段，许多基本问题和概念仍需要在发展中回答和完善。也正因为如此，它为我们跻身科学前沿提供了难得的契机。可喜的是，我国的纳米科技研究与发达国家差距并不明显，在某些方面已经处于前列。具体到纳米细胞生物学研究方面，包括北京大学、武汉大学和湖南大学等高校，以及中科院化学研究所、物理研究所、生物物理研究所和国家纳米科学中心等多家研究机构，先后开展了相关探索，并在国内逐渐形成了具有一定实力的、稳定的跨学科研究队伍，为学科的进一步发展奠定了良好的基础。比如，生物物理所研究人员在生物纳米机器——质子泵的构筑和调控研究方面，近年来已经取得了颇具特色的研究成果。国际科技界同样活跃着一批颇具影响力的华人学者，如美国埃默里大学的聂书明和哈佛大学的谢晓亮等，而他们也正积极参与到国内的科研活动之中。相信随着更多科技人员的参与和努力，我国在纳米细胞生物学方面的研究必将取得更大的突破。

“它山之石，可以为错”，我想这也是科学出版社引入这本专辑的意义所在。

沙印林

2010年冬于北京大学畅春园

序　言

纵观人类文明史，出于探索物质世界的需要，我们人类以智慧进行了各种必要的发明创造，以此深化对自然界的了解，尤其是对超越我们自身感知极限的物质世界的认知。而推动力则源于我们对时间和空间两方面认知需求的持续提高。例如，为了观察远距离物体而发明的各种望远镜，使我们得以发现很远的星云和以光年为单位的远距离行星；而为了研究极小物体发明的显微镜，则促成了微米尺度的生命单元——细胞以及处于纳米尺度的细胞器的发现。然而，探索的终极目标应该是揭示活细胞在原子分辨水平实时的结构与功能。在过去的十年间，技术方法的巨大进步已经开始逼近实现这一目标。围绕在原子分辨水平认知活细胞的实时结构与功能这一目标，本书例举了在近年来所取得的各种相关进展。

从历史的角度看，新的成像技术的发展不仅增加了我们对生物界新的认识，而且在极大程度上关系到人类自身的健康水平。三百年前光学显微镜的发明，作为第一个催化剂，推动人类进入现代细胞生物学与现代医学的纪元。而利用光学显微镜对细胞的发现，无疑是跨入现代细胞生物学与医学的一大步。同时，利用光学显微镜，正常与病变细胞以及病源微生物的结构与形态得以第一次被观察到。随后的二十世纪三十年代，电子显微镜的诞生开创了新的时代。自四十年代中期至五十年代，利用电镜技术，多种亚细胞结构和细胞器的功能被揭示。病毒，作为新的生命形式被首次发现和研究，它与从普通感冒到自身免疫性疾病（AIDS）等多种病患有关。虽然电镜可以在近纳米水平观测生物样本，但样品处理过程中引起的形态改变仍然需要考虑。在随后的二十世纪八十年代，扫描探针显微镜技术的发明进一步将我们对生物界的认知扩展到了近原子层次。作为扫描探针显微镜技术的一种，原子力显微镜有助于克服光学显微镜和电镜技术的局限性，并能够在纳米水平确定活细胞和生物分子在三维空间的结构与动力学特性。光学显微镜的分辨能力取决于所使用的光波的波长，因此光学成像至多可以达到水平分辨率250～300nm（x-y 平面），而纵向（z 轴方向）分辨率则更低。其结果是小于 250～300nm 的细胞结构一直逃避了可视化探测，直至原子力显微镜的发明。在本书中，分别例举了原子力显微镜的各种应用，包括：一种新的细胞结构——“孔体”（porosome）的发现及其在活细胞中结构与动力学的纳米分辨水平的实时研究（第一章）；在纳米分辨水平亚细胞器的结构与动力学的实时研究（第二、三章）；以及第四章中有关硅藻错综复杂的生物矿化研究。与此类似，原子力显微镜也已经用于揭示细胞中膜融合的分子机理（第八章），以及膜结合蛋白的组装与离解（第八、九章）。膜靶向蛋白 SNAP-25 和突触趋化素（t-SNARE），以及分泌小泡结合膜蛋白（VAMP 或 v-SNARE），是参与对峙膜间融合的保守蛋白复合物的一部分。伴随 SNAP-25 与突触趋化素结合，VAMP 和突触趋化素均成为完整膜蛋白。因此，要了解 SNARE 导致的膜融合，需要确定膜结合蛋白 v-SNARE 和 t-SNARE 的相互作用与空间排布方式。理想的状况是，利用 x-射线晶体学提供的膜结合蛋白 SNARE 复合物的原子坐标揭示 v-/t-

SNARE 复合体中原子的空间排布细节。然而，由于 SNARE 的水溶性问题，同时顾及这样的事实，即 v-SNARE 和 t-SNARE 需要分居于相互对峙的膜上，以形成符合生理条件的 SNARE 复合物，目前尚不可能得到膜结合蛋白复合物 v-/t-SNARE 的原子分辨水平的结构细节。另外的选择是利用核磁共振谱，但由于核磁共振技术在分子大小上存在局限性，仍然不能成功解析该蛋白复合物结构。尽管存在以上诸多问题和局限性，原子力显微镜力学谱第一次在纳米分辨水平揭示了膜结合 v-/t-SNARE 复合体在生理缓冲液中的结构、组装和离解过程（第八章）。

以上的事例证明了原子力显微镜技术在增进细胞研究方面的作用和应用范围。同样在本书中也讨论了一些有关细胞结构与功能研究的新的技术途径。比如在第十章中，采用 x-射线吸收谱（XAS）研究了活细胞中金属蛋白的结构和动力学。近年来，XAS 已经成为一种新的有力工具开展细胞中金属离子和含金属生物分子的结构与动力学研究。同步辐射光源提供的 x-射线具有高通量和宽的能量范围，可以实现细胞中单一金属离子的核心电子越迁的选择性激发。因此，这些电子越迁的光谱信号可以用于确定细胞、细胞成分以及生物分子中的金属离子在不同结构分辨程度的化学构筑特点。在高分辨水平实时研究活细胞中蛋白质的折叠、结构和动力学是细胞纳米生物学中的另一个主要阶段。在第十四章中，通过利用一种新型的蛋白转导试剂（QQ-reagent），可以实现在原子分辨水平进行活细胞中蛋白质的折叠、结构和动力学的相关探索。而利用光激活离子通道的纳米操控和标记，目前已经能够远程精细调控神经元行为（第十一章）。定量相位成像（第五章）以及傅立叶成像相关谱（第六章）则对探索细胞的结构与功能提供了新的技术视角。同样地，物质凝聚态的太赫兹研究进一步深化了生物分子的结构与功能的探索。最后，通过与传统技术结合，更多的新技术途径同样有助于细胞结构与功能的探索（第六、八、十一、十五和十六章）。随计算方法的不断更新与提高，原子力显微镜、XAS 和核磁共振技术、蛋白质组学、基因组学和分子动力学模拟，已经成为细胞研究中有力的主导技术和方法，并推动科学研究进入纳米细胞生物学这一新的领域。

Bhanu P. Jena，理学博士

（沙印林　译）

Dedicated in memory of George E. Palade (1912–2008), the father of Modern Cell Biology.

—Bhanu P. Jena

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PREFACE

Throughout history of human civilization, our quest to understand *Nature* has fueled our imagination to make the necessary inventions that further our perception of *Nature*, perceptions beyond the natural limits of our senses. Our constant desire to improving our understanding of time and space has been a powerful driving force. For example, the invention of various telescopes for observing distant objects, and microscopes for studying the very small, has enabled discoveries of distant galaxies and planets light years away, and of the micrometer-size unit of life—the "Cell", and its nanometer-size subcellular organelles. The ultimate goal, however, is the understanding of cellular structure–function at atomic resolution and in real time in live cells. In the past decade, major advances in technology and approach, has come close to realizing this objective. In this book, examples of the various advancements made in recent years, to realizing the ultimate goal of understanding cellular structure–function at atomic resolution and in real time in live cells, are presented.

Throughout history, the development of new imaging tools has provided new insights into our perceptions of the living world and profoundly impacted human health. The invention of the light microscope more than 300 years ago, was the first catalyst, propelling us into the era of modern cell biology and medicine. Using the light microscope, a giant step into the gates of modern cell biology and medicine was made with the discovery of the "Cell". The structure and morphology of normal and diseased cells, and of disease-causing microorganisms, were observed for the first time using the light microscope. Then in the 1930s, with the birth of the electron microscope (EM), dawned a new era. Through the mid 1940s and 1950s, a number of subcellular organelles were discovered and their functions determined using the EM. Viruses, the new life forms, were discovered and studied for the first time, and implicated in diseases ranging from the common cold to autoimmune disease (AIDS). Despite the capability of the EM to image biological samples at near nanometer resolution, sample processing resulting in morphological alterations remained a major concern. Then in the mid 1980s, scanning probe microscopy was invented, further extending our perception of the living world to the near atomic realm. One such scanning probe microscope, the atomic force microscope (AFM), has helped overcome both limitations of light and electron microscopy, enabling determination of the structure and dynamics of live cells and biomolecules in 3D, at near angstrom resolution. The resolving power of the light microscope is dependent on the wavelength of the light used and hence, 250–300 nm in lateral and much less in depth resolution can at best be achieved using light for imaging. As a result, cellular structures measuring less then 250–300 nm in lateral

or depth dimension, had evaded visual detection until invention of the AFM. In this book, the utilization of the AFM in the discovery of a new cellular structure, the "porosome" and its structure and dynamics at nanometer resolution in real time in live cells (Chapter 1), the structure and dynamics of subcellular organelles at nanometer resolution and in real time (Chapters 2 and 3), and in Chapter 4, the examination of the intricate biomineralization in diatoms, is presented. Similarly, the AFM has been utilized to understand the molecular mechanism of membrane fusion in cells (Chapter 8), and the assembly and disassembly of membrane-associated proteins (Chapters 8 and 9). Target membrane proteins, SNAP-25 and syntaxin (t-SNARE) and secretory vesicle-associated membrane protein (VAMP or v-SNARE), are part of the conserved protein complex involved in fusion of opposing bilayers. VAMP and syntaxin are both integral membrane proteins, with the soluble SNAP-25 associating with syntaxin. Therefore, understanding of SNARE-induced membrane fusion required determination of the arrangement and interaction between membrane-associated v- and t-SNARE proteins. Ideally, the atomic coordinates of membrane-associated SNARE complex using X-ray crystallography would provide atomic details of the t-/v-SNARE complex. Such atomic details of membrane-associated t-/v-SNARE complex has not been possible, primarily due to solubility problems of membrane SNAREs, compounded with the fact that v-SNARE and t-SNAREs need to reside in opposing membranes when they meet, to form the appropriate physiologically relevant SNARE complex. The remaining option has been the use of nuclear magnetic resonance spectroscopy (NMR); however, the NMR approach too has not been successful, primarily due to the molecular size limitation of NMR application. Regardless of these set backs and limitations, AFM force spectroscopy has provided for the first time at nm resolution, an understanding of the structure, assembly, and disassembly of the membrane-associated t-/v-SNARE complex in physiological buffer solution (Chapter 8).

The above examples demonstrate the power and scope of the AFM in providing an increased understanding of the cell. Similarly in the book, examples of a number of new and novel approaches in the study of cellular structure-function, is also discussed. In chapter 10 for example, the structure and dynamics of metalloproteins in live cells, has bee investigated using X-ray absorption spectroscopy (XAS). In recent years, XAS has emerged as a new and powerful tool in investigating the structure and dynamics of metals in cells and in metal containing cellular biomolecules. Utilizing the high flux and broad energy range of X-rays supplied by synchrotron light sources, the selective excitation of core electronic transitions in each metal within cells, can be achieved. Spectroscopic signals from these electronic transitions can therefore be used to determine the chemical architecture of metals in cells, in cellular components, and in biomolecules, at varying degrees of structural resolution. Real time investigation of protein folding, structure and dynamics at high resolution in living cells, is the next major step in nano cell biology. In Chapter 14, using a QQ-reagent based protein transduction technology, investigation of protein folding, structure and dynamics, at atomic resolution *in vivo* can be investigated. Today, nano manipulation and tagging using light-activated ion channels, has made

it possible to precisely and remotely regulate activity in neurons (Chapter 11). Quantitative phase imaging (Chapter 5), and Fourier imaging correlation spectroscopy (Chapter 6), now provide novel insights into our understanding of cellular structure–function. Similarly, THz investigation of condensed phase studies, provide further understanding into the structure–function of biomolecules. Lately, a plethora of novel approaches, combined with conventional tools and techniques, provide a better understanding of cellular structure–function (Chapters 6, 8, 11, 15, and 16). Using new and improved computational resources; AFM, XAS, NMR, proteomics, genomics, and molecular dynamic simulation, have become leading and powerful tools and approaches in the study of the cell, and investigation into the new field of "*Nano Cell Biology*".

Bhanu P. Jena, Ph.D., D.Sc.

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