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A decade of molecular cell biology: achievements and challenges

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Abstract

Nature Reviews Molecular Cell Biology celebrated its 10-year anniversary during this past year with a series of specially commissioned articles. To complement this, here we have asked researchers from across the field for their insights into how molecular cell biology research has evolved during this past decade, the key concepts that have emerged and the most promising interfaces that have developed. Their comments highlight the broad impact that particular advances have had, some of the basic understanding that we still require, and the collaborative approaches that will be essential for driving the field forward.

What do you feel have been the most significant, and perhaps most surprising, new concepts to emerge in molecular cell biology during the past decade? Has this progress been enabled by a particular technical advance?

Asifa Akhtar. There have been a number of important concepts that have emerged. One that particularly jumps to mind is the importance of epigenetics in gene regulation. The field of epigenetics has flourished over the past 10 years. It is clear that chromatin provides an ideal platform for various posttranslational modifications on DNA and histones, which act as a signalling platform for various cellular processes. I also think that the discovery that a combination of four transcription factors can induce a pluripotent state was phenomenal and has stimulated a lot of research in the stem cell field[1]. Last, but not least, the involvement of non-coding RNAs in various cellular and nuclear processes is totally fascinating. The mechanisms by which long non-coding RNAs regulate gene expression await exciting discoveries in the coming years.

Elaine Fuchs. For the stem cell field, there is no question that the findings of Shinya Yamanaka and his co-worker Kazutoshi Takahashi were paradigm-shifting. Their work reported the creation of induced pluripotent stem (iPS) cells from mouse skin fibroblasts when cultured in embryonic stem cell (ESC) conditions[1]. It was remarkable that transient overexpression of a mere four transcription factors, OCT4, SOX2, MYC and Krüppel-like factor 4 (KLF4) — all naturally expressed by ESCs — could achieve this dramatic dedifferentiation of fibroblasts. This finding has allowed researchers to derive patient-tailored iPS cells to study the biology of a host of different human diseases — a first step, but a major one, for the future development of new drugs and treatments in medicine.

Tim Mitchison. Reaction–diffusion gradients specifying positional information inside cells. Gradients of signalling molecules were long known in developmental biology and paracrine physiology. But gradients inside cells being used as a spatial organizing system is a new concept. Bicoid, a classic developmental morphogen, diffuses inside a syncytium, but this is a special case. Gradients of RAN•GTP from mitotic chromatin and of Aurora B activity from chromatin in M phase and midzones in cytokinesis are classic cellular signals that we now know organize space inside cells using a reaction–diffusion mechanism. I attribute this concept to Eric Karsenti, who mooted the idea in the mid 1980s for signals diffusing away from DNA in eggs. However, it wasn't proven until the development of fluorescence resonance energy transfer (FRET)-based activity biosensors in the past decade[2,3]. In general, fluorescence sensors of biochemical activity are a very important development.

Reuben J. Shaw. One area close to our own work is the unexpected re-emergence of metabolism and its relationship to growth control and cancer. Advances in autophagy continue to amaze me in terms of how little basic information we actually have on how a cell works. Autophagy regulators are highly conserved proteins in a central cell biological

process that is deregulated in common human diseases, yet much of the biochemical framework for this process has been decoded only recently. Other newly decoded central regulators and processes, ranging from cilia to sirtuins, microRNAs (miRNAs) and pathways such as those involving Hippo and mammalian target of rapamycin (mTOR), underlying so much biology, have changed half of what we know. These are very exciting times.

Daniel St Johnston. Several surprising concepts have emerged during the past decade: first, the amazing extent to which basic cell biological processes have been conserved during the evolution of eukaryotes; second, how much gene regulation is post-transcriptional, particularly through small non-coding RNAs; third, how basic cellular processes, such as endocytic trafficking, microtubule dynamics or mitochondrial behaviour are modulated during the course of normal development; and last, the wide range of cell biological and developmental events that are regulated in response to cellular stresses, such as DNA damage or nutrient deprivation, and how these are used as signals during normal development.

The most important technical advances have been high-throughput sequencing, which has provided the complete sequence of many genomes, and the use of RNA interference (RNAi) to knock down gene function.

Andreas Strasser. One important concept to emerge is the ability to reprogramme differentiated cells, such as fibroblasts or hepatocytes, to assume a pluripotent stem cell fate. Another key finding has been the discovery that signal transducers undergo complex processes of modification by different forms of ubiquitin linkages and that these regulate cellular responses to extracellular signals, such as ligands of the tumour necrosis factor (TNF) family. In addition, an important result has been the discovery that caspase 8 regulates both apoptosis and another cell death process, termed necroptosis. It will now be important to determine the roles of necroptosis in cell death processes that are thought to shape embryonic development but are not affected by mutations that block apoptosis. Moreover, the mechanism by which caspase 8 prevents receptor-interacting protein 1 (RIP1)- and RIP3-mediated necroptosis is now an area of immense interest.

Susan Taylor. Genomic science has transformed the way we think about biology and provides us with a new paradigm for asking biological questions and for thinking about evolution. Sequencing technology has advanced at an extraordinary pace, as has computing, so that sequencing whole genomes is becoming rapid and inexpensive. This has changed the face of biology. The human microbiome and our dramatic co-evolution with microbes is one of the most surprising discoveries to emerge from genome science. In parallel, and also of comparable magnitude, is the recognition of the role that small RNA molecules have and their enormous importance in regulating biology.

Claire E. Walczak. The past 10 years have been remarkable in terms of our understanding of genome organization, chromatin structure and gene expression, which provide the foundation for specifying individual cell function. This information has also provided the basis for many genome-wide studies looking at a multitude of biological processes and disease states. Such studies have provided fundamental new insights into epigenetics, have elucidated a molecular understanding of altered gene regulation in disease, and have enabled fundamental new discoveries, such as RNAi and the existence of miRNAs in the genome.

Marino Zerial. In the past decade, we have progressively shifted our view and approaches drastically towards a genomic perspective. Today, our research of biological processes is no longer focused on single genes or proteins but tends to widen to the complexes, pathways or even systems level. Owing to this change in dimensionality, we have ‘changed gear’ and

routinely benefit from comparing species, interrogating genomes and manipulating cells and organisms. This was unthinkable in the 1990s. For example, consider how RNAi has changed our approach to exploring the function of genes. In general, the genomic revolution has disclosed a horizon of interesting problems, such as the role of both coding and non-coding RNAs, to name one.

There has been increasing collaboration between different research communities both within, and outside, cell biology. Where do you think the most interesting interfaces in molecular cell biology reside, and what do you envisage the most fruitful collaborations will be in the future?

A.A. Indeed, in this post-genomic era, the way we do research has changed dramatically. On average, papers have a more interdisciplinary and collaborative flavour, especially in combining biochemical and genomic analyses. In the future, I can foresee even more fruitful collaborations between cell and molecular biologists and bioinformaticians or even physicists. In fact, I think the next generation of scientists are already on the way who will perform both wet and dry laboratory research equally well.

E.F. I find the interface between human genetics, cell biology and the pharmaceutical and biotechnology industries to be the most exciting. The ability to rapidly sequence many human cancer samples has led to the identification of frequent mutations in particular types of cancer. The advances in small-molecule screening and design have led to fruitful collaborations between basic and pharmaceutical chemists, as they begin to design drugs that target only the mutant form of the protein and not its wild-type counterpart. An example is the recent development of inhibitors against the Val600Glu mutation in BRAF, a frequent mutation in melanomas[4,5]. While tumour resistance still makes eradication problematic, application of this approach to tumour resistance mutations should lead to drugs that can overcome the tumour cell resistance. With a bit of vision towards the future, we can begin to imagine drug cocktails that will make many more cancers treatable.

T.M. The development of new microscopy technology is currently extremely exciting, and has been for two decades or more. This includes new instrumentation, which typically involves physicists, and new probes, which often involves chemists. Super-resolution is one exciting direction (photo-activated localization microscopy (PALM), stochastic optical reconstruction microscopy (STORM) and stimulated emission depletion (STED))[6–8]. Activity biosensors is another[2,3]. Intravital imaging in mice and humans is yet another.

The success of mathematical modelling has been more mixed. I am optimistic that it will help us truly understand collective protein behaviour in the future but, so far, I think the impact has been modest. One big problem is groups saying, “Our model works, therefore we have solved the problem”. This is rarely true, and questionable assumptions are often hidden. But we do know that human intuition alone cannot explain collective protein behaviour in complex systems, and there seems to be no alternative to formal modelling. But, we do have to get it better integrated and be more critical.

Finally, DNA sequencing is getting cheaper by the day, and this will have a huge impact. If you can apply this resource to your question, you will make rapid progress. It will also greatly enable work on non-traditional organisms, which opens up all of biology for molecular cell biology approaches.

R.J.S. There have been incredible breakthroughs by technology-driven laboratories with expertise in physics, microscopy and mass spectrometry, which have revolutionized the ability to detect and quantify protein abundance, modifications and interactions, as well as the concentrations of intracellular metabolites that would have been unimaginable 10 years

ago. This has also been coupled with advances in RNAi technology, DNA sequencing, ChIP–seq (chromatin immunoprecipitation followed by sequencing) and other techniques that bring high-throughput approaches to cell biology laboratories. Collaborations among adept practitioners using these disparate technologies to decode tissue-specific regulators and rate-limiting pathway components will uncover much fundamental cell biology as well as new targets for many different disease states.

D. St J. Cell biological research is becoming increasingly quantitative, and this has stimulated exciting collaborations with mathematicians and physicists in diverse areas, for example to measure forces in biological systems, to model morphogenetic events and to automate image analysis. Input from the physical sciences has also played an important role in the development of super-resolution microscopy, which has the potential to revolutionize cell biology if and when it can be improved to image faster and deeper inside cells.

A.S. Interactions between bioinformaticians and cellular and molecular biologists have been highly productive, for example by allowing one to make sense out of large data sets, such as gene expression profiles. Interactions between structural biologists, medicinal chemists and cell biologists have allowed us to define complex interactions of proteins in cell signalling, such as the functions of the B cell lymphoma 2 (BCL-2) family members in apoptosis. Importantly, such interdisciplinary interactions have facilitated the development of small molecules to manipulate these processes in a therapeutic setting, such as the treatment of certain cancers.

S.T. Building bridges between computational science and experimental biology is one of our great opportunities and also one of our greatest challenges. There are enormous opportunities for bridging biology with theory and computer science, as well as with translational medicine. Advances in computing have allowed us to gather enormous amounts of data; however, the relevance of the data is compromised without a mechanistic understanding of biological systems. It is absolutely essential to bring these communities together so that we find ways to truly speak a common language. Only in this way can we achieve a comprehensive view of biological systems.

C.E.W. Even only 10 years ago, cell biology was largely a ‘fuzzy’ science, in which we looked at pretty pictures and described what we saw. Quantitative approaches, aided by advances in imaging, have transformed the field to a more quantitative science. The development of mathematical models for biological processes has grown increasingly more complex, offering new insight into protein function. In the future, we need to increase collaboration with chemists and physicists utilizing nanotechnology to visualize and perturb proteins on smaller and smaller scales. Computer scientists are essential to help us organize, process and analyse the large datasets being generated by high-throughput methods.

M.Z. Biological research today makes use of more quantitative approaches than before. For example, imaging and image analysis can be very quantitative, sensitive and precise, and thus are tremendously powerful for exploring biological mechanisms in time and space. This makes the collaboration with theoreticians particularly productive. Biologists need to work with mathematicians, physicists and engineers interested in biological problems because they can help us to understand mechanisms in a more precise and predictive fashion. Previously, our problem was the ability to identify some components that could give us clues into molecular mechanisms. Now that we can get to such components relatively easily (for example, with ‘omics’), our problem becomes how to understand the ways in which the structure and functional properties of biological systems emerge from the interplay of individual components. For this, we need the support of theory.

What, in your view, are the most pressing questions and key challenges for cell biologists moving forward?

A.A. The dynamics and quantitative nature of how various pathways and macromolecular complexes function remain poorly understood. We are also beginning to appreciate that spatial and temporal control contribute important regulatory steps in gene regulation. The same molecule in different cellular compartments may have very different regulatory functions, which could be missed during biochemical analyses. If we can gear our research to go from qualitative to quantitative biology and understand the real dynamics of our favourite molecules *in vivo*, we will make a great leap in our understanding of various cellular pathways.

E.F. The most pressing questions in my field are in many ways no different than they were 20–30 years ago, but the answers are closer at hand. How do stem cells build tissues during normal homeostasis and wound repair, and how does this go awry in human diseases, including cancers? And how can we exploit this information to understand the bases of these different diseases and develop new and improved therapies for the treatment of these disorders? With the recombinant DNA technology revolution of the early 1980s and the human genome revolution at the turn of the century, the interface between basic science and medicine is closing at a pace we never imagined possible as students. The tools and technologies available to address fundamental biological questions are advancing at a ferocious rate. The challenge ahead will be to ask the right questions and creatively develop strategies that exploit these tools to bridge this gap and revolutionize medicine.

R.J.S. A big challenge going forward comes out of this explosion of data from different systems: bridging the omics studies (RNAi screens, ChIP–seq, phosphoproteomes and mass spectrometry interactomes) to define what the key rate-limiting proteins in any biological process are. The world still needs careful mechanistic dissection of individual proteins and functions, which sometimes gets lost amidst the push for larger and larger datasets. Taking the findings in cellular systems and then bridging that to the physiology and pathology of diseases in the intact higher organism also remains a key challenge.

D. St J. Most recent cell biology has focused on a relatively small number of cell types (most often, unpolarized, transformed tissue culture cells) and has largely overlooked the astonishing array of different cell types with specialized functions that occur *in vivo*. I think that one of the key challenges for the future is to develop better ways of performing *in vivo* cell biology to examine cellular behaviours in the context of organs and tissues. The ability to induce iPS cells to form organs in culture will be an enormous help for this type of work.

A.S. One challenge is elucidating the precise definition of how cellular differentiation and functional activation are controlled; that is, how the many transcriptional regulators, modifications to the genome (for example, through methylation) and posttranscriptional regulatory processes (for example, through the impact of miRNAs) interact to regulate stepwise changes towards a differentiated state. Another is defining the mechanisms that regulate non-apoptotic, but still genetically programmed, cell death pathways and the definition of their role in normal physiology (for example, during embryonic development and tissue homeostasis in adulthood).

S.T. The biggest challenge for biology is always to ask the right question, and this is even more important now as technologies advance so rapidly. In our frenzy to collect more and more data, we need to learn how to ask the right questions and how to extract useful information from that data. In parallel with systems biology, we must have a mechanistic understanding of biology. Without understanding the underlying biochemical principles, the data mean little. Just as we need classical physiology to understand how molecules work in

whole animals, we need biochemistry to have a true mechanistic understanding of biological events.

C.E.W. While the genomic revolution has provided us with a wealth of potentially important molecules, the large-scale functional genomics screens only scratch the surface of understanding the mechanisms by which these proteins act. The challenge is to develop creative approaches to answer the most fundamental biological questions. For example, although proteomic approaches have identified all of the components of the mitotic spindle and genome-wide screens have identified an array of molecules that affect the mitotic spindle, we still do not understand the fundamental mechanism by which each chromosome moves to the spindle equator and then is partitioned to the daughter cells.

M.Z. Cell biology must move to tissues and organisms. An outstanding problem is bridging between scales. Understanding how cellular components form complexes, how these assemble into organelles and how organelles form cells, which build organs and organisms, poses enormous technical and conceptual challenges. The integration of biological processes is one of the most difficult problems we face. Solving these problems requires trespassing across the traditional borders between fields and developing new experimental and analytical methods. At present, we can explain only small parts of biological mechanisms: we see a few pieces of a puzzle, but for the whole picture we must draw in complexity. There are no current solutions at the modelling or computational level. This problem requires the development of new theories.

What would you consider to be the main bottlenecks for the productivity of your research and what advice would you give to young researchers facing these challenges?

A.A. Despite technical advances, such as high-throughput sequencing strategies, which have been tremendous in providing us with a global view relatively rapidly, the real bottleneck remains the in-depth analysis of data from these strategies and how to make biological sense out of such information. I also think the challenge remains to understand how various biological pathways work mechanistically and, even more importantly, how various pathways are interconnected. These are challenges for all generations of scientists. For young laboratories, one of the major challenges is to hire the right group of people and to focus on a particular biological question. My advice would be to use a multidisciplinary approach to address the questions of interest, as this provides one with the possibility to look at the question from different angles and may reveal unexpected and exciting findings.

E.F. In the United States, the main bottleneck is the precarious funding climate we face and the diminished emphasis our country places on higher education. Our country has spent decades investing in biomedical research and we are now poised to capitalize on this foundation and make major breakthroughs in the coming decades. It is paramount that we work harder to educate policy makers and the public about the time it takes to translate scientific discoveries into cures. I am optimistic that we can do so, and I would encourage young researchers to be optimistic as well, to pursue their passion for science but also to become involved in efforts to communicate with policy makers and the public who hold the strings to our future.

T.M. Funding is a major bottleneck everywhere, and it particularly affects young scientists. One huge challenge is proving our worth to society, which we must do if we expect to be funded by taxpayers' money. The huge progress in molecular cell biology in the past two decades has not translated into a whole lot of improvement in the human condition — for example, new ways of preventing and treating disease. I believe basic science is having, and will have, that impact, but over long time periods and, often, in unpredictable ways. Solving

this problem requires that some bright young people (but not all — basic progress is as important as ever) take the road of: first, translating basic research into useful applications, which in my mind includes synthetic biology as well as more conventional ideas like drugs and stem cell-based organ replacements; and second, educating and energizing the public, which includes innovating at all stages of conventional education as well as public outreach, political action and internet-based science activity.

My advice to young scientists is to avoid the road well travelled. There is no surefire route to success in sciences. But if you take the common road of doing what your advisor and her colleagues already do, you are guaranteed to end up in a crowded field in which it is hard to compete for resources and gain independent recognition. You need to take risks — in approach, in system and in questions.

R.J.S. Ironically, in the face of the kinds of technologies that have been developed for cost-effective RNAi screens and full proteomic mass spectrometry analyses of all cellular proteins and metabolites, one unmet need that is still rate-limiting in nearly every area of cell biology research is having tools and reagents that can selectively visualize pools of a given protein with specific post-translational modifications (for example, acetylation, sumoylation and phosphorylation) in intact cells and organisms. My advice to young scientists would be to explore areas at those interfaces between fields and always be incorporating new techniques and ways of thinking about a biological problem.

D. St J. Apart from the usual ones of too much bureaucracy and too little funding, one of the major difficulties we face in the laboratory is how to examine the functions of proteins that have multiple roles in the same cell lineage. Although there are a few specific tricks that allow one to knock out the function of a protein at a specific place or time, most of these actually knock out the gene and not the protein, leaving the problem of perdurance. It would be a huge help to have a standard way of engineering conditional mutant forms of proteins that are either light or heat sensitive.

My advice to young scientists is to not assume that everything that has been published is correct and that it is better to tackle interesting questions that are hard than minor questions that are easy.

A.S. First, I believe that it is important to work on a problem that you are passionate about (that is, for which you really, really want to be the first to know the answers). Second, it is a great joy to work in an environment that is highly collaborative and collegial. Nobody can cover all areas of expertise that are necessary to tackle ‘big issues’. Therefore, having ready access, as a cellular or molecular biologist, to structural biologists and bioinformaticians who are eager to collaborate is a great boost for your ability to answer important questions. Finally, when choosing your postdoctoral position, it is in my opinion a good idea to join a group that desperately needs your expertise and has projects and/or techniques on offer that you want to learn. This will create a mutually beneficial or ‘symbiotic’ relationship, whereas joining a research programme that already has all the expertise that you can offer is like ‘shipping coals to Newcastle’.

S.T. Formulate your questions carefully and then delve deeply into your system. Do not be afraid of collaborations and of learning new technologies and new systems. Do not fear reaching out. A major bottleneck for all biological research in the United States now is funding of RO1 investigator-initiated grants. The US National Institutes of Health have nurtured an explosion of biological discoveries over the past few decades, and these discoveries are having an enormous, and often unanticipated, impact on our understanding of disease. We have, unquestionably, been the dominant player in the international

community. Other countries, however, are now outpacing us in their funding and we will have trouble maintaining our eminence and dominance.

C.E.W. Carrying out studies that will have a sustained impact requires an ever-increasing amount of multidisciplinary resources, including people, expertise, equipment and funding. Our educational system is not keeping pace with the rapid development of new technologies and still maintains fairly traditional disciplines. This makes it challenging to recruit young scientists who are willing to break new ground to make the exciting new discoveries. My advice to young researchers is to take every opportunity available to learn and discover, and never forget to take time to just think and reflect about what is interesting and cool.

M.Z. My strong advice to young researchers is to think in a truly multidisciplinary way and to go to institutes which can support this approach. Addressing a problem from different sides is essential. Good funding is not everything: I would also encourage young scientists to choose institutes where they can get good mentoring and be stimulated and challenged by faculty members who demonstrate true interest in their work. Importantly, treasure the value of central facilities, available to everyone and capable of supporting research beyond what a single laboratory can do. This kind of support raises the level of ambition and productivity of a young starting group more than any seemingly rich ‘start-up package’.

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Tim Mitchison obtained a biochemistry degree at Oxford University, UK, and then moved to the laboratory of Marc Kirschner for his Ph.D. thesis, during which he purified tubulin from centrosomes and characterized the ‘dynamic instability’ that underlies microtubule growth. He started his own group at the University of California, San Francisco (UCSF), USA, in 1988 and 9 years later moved to the systems biology department at Harvard Medical School, Boston, Massachusetts, USA. He became the President of the American Society for Cell Biology in 2010.

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Andreas Strasser is Joint Head of the Molecular Genetics of Cancer Division at The Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia. His research is focused on programmed cell death and how defects in this process cause cancer or autoimmune disease and affect the response of tumour cells to anticancer therapy. Key discoveries have been: that abnormalities in cell death control can cause cancer or autoimmune disease; that B cell lymphoma 2 (BCL-2) and death receptors regulate distinct pathways to apoptosis; the pro-apoptotic BCL-2 homology 3 (BH3)-only proteins and that they are essential for initiation of programmed cell death; that BCL-2-interacting mediator of cell death (BIM; also known as BCL-2L11) is required for negative selection of autoreactive thymocytes and mature T cells; and that p53 upregulated modulator of apoptosis (PUMA; also known as BBC3) and NOXA (also known as PMAIP1) are essential for DNA damage-induced apoptosis mediated by the tumour suppressor p53. Current efforts include the development of antagonists of pro-survival proteins for cancer therapy.

Susan Taylor is an HHMI investigator at the University of California, San Diego (UCSD), USA, in the Departments of Pharmacology and Chemistry and Biochemistry. She received her Ph.D. in physiological chemistry from The Johns Hopkins University, Baltimore, Maryland, USA, working with Edward Heath. For her postdoctoral research, she worked first with Brian Hartley at the Medical Research Council Laboratory of Molecular Biology in Cambridge, UK, and then with Nathan Kaplan at UCSD. Her research focuses on the structure and function of protein kinases, in particular on cyclic AMP-dependent protein kinases, which serve as a prototype for the large protein kinase superfamily. She merges biophysics and structural biology with cell biology and imaging to study not only the structures of the protein kinase A (PKA) regulatory and catalytic subunits but also the targeting of PKA to macromolecular complexes.

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Marino Zerial graduated in biology at the University of Trieste, Italy, in 1982 with a thesis on lysosomal storage disorders. He gained postdoctoral experience at the Institute

J. Monod, Paris, France, on the organization of human genome and at the EMBL on the biosynthesis and endocytosis of transferrin receptor. He became an EMBL Research Group Leader in 1991, when he started his work on the molecular regulation of endocytosis, focusing on the function of RAB GTPases. In 1998, he became Max Planck Director and co-founder of the Max Planck Institute for Molecular Cell Biology and Genetics (MPI-CBG), Dresden, Germany.

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