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Visions of the future of molecular cell biology

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To celebrate the journal's 25th anniversary, we asked 13 researchers to offer a glimpse of what their research field might look like in 2050. They consider how technological breakthroughs — for example, artificial intelligence-powered virtual cells — could transform our understanding of how molecules, organelles and cells behave in different contexts, revolutionize therapies and enable the design of resilient crops.

From cell biology to clinical frontiers in lysosome research

Monther Abu-Remaileh. Lysosomes are small yet essential organelles that function as a metabolic hub in the cell by recycling macromolecules, clearing damaged organelles and signalling nutrient state to maintain cellular homeostasis. Mutations in lysosomal genes cause lysosomal storage diseases, and lysosomal dysfunction is implicated in cancer and neurodegeneration – spurring major efforts to pursue them as drug targets.

The complexity of the lysosome, including its enzyme-packed lumen and transporter-decorated membrane, makes it an attractive system for interdisciplinary research. Nearly 8 years ago, we developed the LysoIP method that, with high-resolution mass spectrometry, enabled us and others to uncover the roles of lysosomal genes in disease and study lysosomal dynamics.

Innovative technologies are a major driver of biological breakthroughs. Advancements in single-organelle microfluidics, mass spectrometry and high-resolution spatial omics will allow us to profile single lysosomes within tissues, uncovering heterogeneity and context-specific roles.

Near-atomic resolution microscopy with live imaging, especially at a level similar to cryo-electron tomography, is a major scientific dream. If realized, it would allow real-time observation of molecular interactions within individual lysosomes and with other organelles, and enable tracking of enzyme and transport activities, as well as the assembly and disassembly of lysosomal protein complexes, revealing mechanisms of function and disease.

As in many areas of biology, artificial intelligence (AI) will drive novel insights into lysosomal dynamics and predict lysosomal responses to external cues and disease states. I believe that modelling their behaviour in a 'virtual cell' will further help uncover molecular players that transmit signals to and from lysosomes to coordinate metabolic flux and maintain cellular homeostasis.

Finally, therapeutic targeting of the lysosome by inhibiting or enhancing its function is being explored across diseases ranging from cancer to neurodegeneration. In the next 25 years, more lysosomal targets will emerge, and lysosomal modulation will reshape how we understand and treat human disease.

Biophysics and AI are the next big wave in ovarian biology

Chii Jou Chan. It is an exciting time for the field of ovarian biology, which is rapidly evolving! Although it is always hard to speculate about the future, I believe that recent advances in biophysics, biophotonics and AI will provide an integrative approach to address many fundamental questions in the field that remain outstanding.

First, the development of new biophysical tools to probe and manipulate tissue mechanics will help us understand how the ovarian mechano-microenvironment shapes follicle growth and fate. Integration of these tools with advanced biochemical sensing techniques – such as multiplexed biosensors, nanoscale probes or Raman-based spectroscopic detection – will allow us to map hormone gradients, metabolic activity and local molecular signalling events with high specificity and sensitivity. Second, the development of deep-tissue imaging techniques will allow us to study ovarian dynamics in vivo with unprecedented spatio-temporal resolution. Miniature microscopes, engineered to be implanted into human bodies, will enable the direct visualization of reproductive processes such as ovulation and fertilization in vivo. These technological breakthroughs will revolutionize assisted reproductive technology, leading

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to better treatment of infertility and ovarian diseases.

Another area where I imagine significant progress in the coming decades is the use of AI in ovarian biology and fertility. Here, machine learning approaches, such as graph neural networks, will be used to mine the morphodynamic atlas of ovarian cycles, thereby uncovering hidden biophysical principles governing robust selective follicle growth, death and ovulation. This will allow us to develop mathematical models to simulate and predict ovarian dysfunctions during ageing and disease progression. Finally, we still know very little of how mammalian germ cells become sperms or eggs. Given the distinct tissue architectural difference in the testes and ovary, it is plausible that tissue mechanics may influence primordial germ cell-fate decision. Here, applying biophysical approaches, in combination with recent breakthroughs in in vitro gametogenesis, may unravel the mechano-biological principles regulating gamete maturation and sex differentiation.

Unleashing RNA to transform biomedicine

Polly Leilei Chen. RNA molecules are enormously diverse in their sequence, structure and cellular compartmentalization. Moreover, RNA molecules exhibit great diversity owing to cell-type-specific expression in different tissues. In 25 years, the fields of RNA biology and RNA therapeutics will be transformed beyond recognition, propelled by unprecedented insights into the complexity and dynamic regulation of RNA molecules.

Building on the foundation laid by the Human Genome Project, the next decades will witness the establishment of comprehensive 'reference' (epi)transcriptomes for specific cell types and physiological or disease conditions, spanning humans, viruses and vital model organisms. Technical breakthroughs synergized with AI, will enable the emergence of technologies that can visualize and interpret the full landscape of RNA chemical modifications (the epitranscriptome), dynamic RNA structures and regulatory networks at single-cell and even subcellular resolution, in real time within living cells and tissues.

This revolution will fundamentally shift RNA biology from a descriptive to a predictive discipline that can anticipate cellular behaviour, disease progression and therapeutic response solely from integrated RNA profiles. Specifically, a deeper understanding will emerge from elucidating how RNA molecules interact with diverse RNA-binding proteins, how their structures dynamically fold and refold, and how chemical modifications fine-tune their fate and function.

Many of today's formidable challenges in RNA therapeutics stem from difficulties such as the instability of RNA molecules in biological environments, inefficient and nonspecific delivery to target tissues, off-target effects that can compromise treatment safety and efficacy, and unwanted immune activation. Addressing these obstacles will require continued innovation in RNA chemistry, nanoparticle engineering and tissue-specific targeting strategies. These advances will enable a comprehensive grasp of the pharmacodynamics and pharmacokinetics of RNA drugs, allowing for safe, predictable and efficient delivery to any desired cell type. Precision RNA-based interventions will become routine and widely accessible, setting new standards for treating a wide spectrum of diseases, from rare genetic disorders to prevalent cancers and neurodegenerative conditions. Ultimately, as the boundaries between RNA biology and therapeutics dissolve, RNA will be recognized not merely as a messenger, but as a fully engineerable, versatile tool for diagnosis, prevention and transformative treatment in medicine.

Unlocking plant potential through engineering

Gozde S. Demirer. Plants are central to solving today's greatest global challenges in food

The contributors

Monther Abu-Remaileh is a biologist and engineer at Stanford University. His laboratory develops and applies quantitative tools to study lysosomal pathways and subcellular metabolism. He is recognized for uncovering molecular mechanisms of metabolic adaptation and lysosomal dysfunction in neurodegenerative diseases.

Chii Jou Chan is a biophysicist and assistant professor in the Mechanobiology Institute at National University of Singapore. His research aims to understand how tissue mechanics and fluid stress regulate mammalian folliculogenesis and ovulatory dynamics during development and ageing, using interdisciplinary approaches integrating biophysics, advanced imaging and computational modelling.

Polly Leilei Chen is an associate professor at the National University of Singapore. A cancer and RNA biologist with over 15 years of experience, she investigates RNA changes in cancer and develops RNA therapeutics. Polly has a key leadership role in advancing cancer and RNA research in Singapore.

Gozde Demirer is an assistant professor of chemical engineering at the California Institute of Technology, USA. Her group's interdisciplinary research develops various tools for plant genome and microbe engineering, working at the intersection of novel nanomaterials, synthetic biology and plant–microbe interactions.

Ana Fiszbein is a molecular and computational biologist at Boston University. Her research centres on splicing, transcription dynamics and RNA therapeutics. Her laboratory integrates high-throughput functional genomics, bioinformatics and molecular biology to investigate how RNA processing shapes gene expression. Her recent work focuses on developing algorithms to predict the impact of splicing disruptions and on designing RNA-based therapies to correct them.

Florian Jug received his PhD in computational neuroscience from ETH Zurich. At Human Technopole in Milan, he develops AI methods for the life sciences. His research focuses on generative models, multimodal data integration, and uncertainty quantification to bridge molecular, cellular, and tissue scales. By advancing AI as a trusted partner for biology, his overarching goal is to elevate the rate of scientific discovery through the methods and tools his team develops.

Ana Victoria Lechuga-Vieco is a junior group leader at IRB Barcelona's Ageing and Metabolism Programme. Her laboratory focuses on mitochondrial biology, intercellular signalling and tissue regeneration, exploring how mitochondrial quality control and immune cell metabolism in ageing and disease can drive targeted therapies for preserving energy-dependent tissues.

Raphaëlle Luisier has degrees in bioengineering and bioinformatics. Her research focuses on studying RNA regulation and function in complex human disorders, such as cancer and neurodegeneration. To this end, her group is developing cutting-edge AI technologies for the integrative analysis of molecular, imaging and clinical data.

Julia Pagan studies protein degradation pathways, mitophagy and mitochondrial quality control at the University of Queensland, investigating how these processes safeguard cellular function in health and disease. Her team integrates advanced imaging, molecular biology and omics approaches to uncover the mechanisms that regulate mitochondrial turnover.

Benjamin Sabari is an assistant professor at UT Southwestern Medical Center. His laboratory investigates how the spatial organization of the nucleus regulates gene expression, with a focus on the role of transcriptional condensates in development and disease.

Sichen (Susan) Shao is an associate professor in the Department of Cell Biology at Harvard Medical School and an HHMI investigator. Her laboratory investigates molecular mechanisms of protein biosynthesis and quality control using approaches integrating biochemistry, cell biology and structural biology.

Liming Sun is a principal investigator at the Center for Excellence in Molecular Cell Science (CEMCS), Chinese Academy of Sciences. Her laboratory combines mouse genetics with molecular biology, cell biology and biochemistry techniques to decipher the molecular regulation of necroptosis signalling that balances cell survival and death, and to investigate the beneficial roles of necroptosis in tissue regeneration — a long-overlooked area.

Jan J. Żylicz is a stem cell biologist and an associate professor at reNEW Copenhagen. His laboratory focuses on how mammalian embryos interact with their environment, particularly how metabolism is coupled with epigenetics and cell-state changes. His team has recently uncovered metabolic principles of implantation and its links to histone acetylation.

security, climate resilience and sustainability. Their remarkable intrinsic capabilities, including carbon fixation, stress resilience and biosynthesis of complex molecules, can be further enhanced through genetic engineering. Yet current genome engineering methods remain slow, inefficient and can be applied only to a limited number of species.

In the next 25 years, I envision we will be able to rapidly and precisely rewrite the genome and epigenome of any plant species. A major hurdle today — biomolecule delivery and transformation — will no longer depend on regeneration in tissue culture, which is currently required because of our inability to access and edit plant stem cells or germline cells. Emerging technologies, particularly nanoparticles, will enable direct delivery of any biomolecules to previously inaccessible cells, allowing transient gene expression modulation for precise and heritable genome engineering. This will unlock the ability to engineer virtually any plant species for any desired trait.

Alongside delivery innovations, the genome engineering toolkit will dramatically expand. New modalities are being discovered at an unprecedented pace, and I anticipate that targeted insertion of large DNA sequences into plant chromosomes, a major current limitation, will become routine in 25 years. Among the most promising emerging technologies of prime editing, recombinases and transposases, I anticipate site-specific retroelements, such as R2, hold the greatest potential for efficient, precise and large DNA insertions into targeted genomic locations. When combined with nanoparticle delivery, these tools could transform plant engineering by enabling insertion of any DNA sequence, of any length, into any plant genome for enhancing existing functions or introducing entirely new-to-nature capabilities. Of these future applications, growing crops that use resources more efficiency, requiring significantly less freshwater and fertilizers, could have one of the greatest societal impacts, addressing the urgent need for sustainable agriculture in the face of climate change and resource scarcity.

With the convergence of programmable delivery, precision genome editing, and systems-level design empowered by AI/machine learning and computational modelling, plant engineering will evolve from incremental trait improvement to rational, predictive design of crops tailored to future ecological and societal needs.

Splicing-based personalized therapeutics

Ana Fiszbein. Over the past 25 years, our understanding of RNA splicing has been revolutionized by the Human Genome Project and next-generation sequencing technologies. These breakthroughs have enabled us to study splicing across species, individuals and tissues at single-cell resolution, and for all genes at the same time. Splicing disruptions have been found to contribute to a wide range of diseases, from monogenic disorders to cancer and neurodegeneration. In particular, splicing defects have emerged as drivers of rare diseases, which collectively affect more than 400 million people worldwide — many of which remain undiagnosed despite genomic testing. The introduction of RNA sequencing as a complementary diagnostic tool when genomic testing fails has been a game changer. But it is only the beginning.

In most patients, we are not able to interpret the physiological consequences of splicing changes. Even when we can identify a mutation that alters splicing, we often cannot explain how it leads to disease. This gap between molecular diagnosis and clinical application leaves patients and their families without answers and causes delays in life-changing care.

In the next 25 years, I believe an important breakthrough will be the ability to interpret — and then therapeutically target — splicing dysregulation. Progress will come from the intersection of computational biology and experimental science: high-throughput transcriptomics and deep learning will allow us to predict function and move accurately from genotype to phenotype.

In parallel, RNA therapeutics — from vaccines to antisense oligonucleotides — will evolve from niche treatments into mainstream. Splicing-switching antisense oligonucleotides will be available not only for common diseases, but also as '$n = 1$' treatments tailored to individuals. This shift will require stronger partnerships between scientists, clinicians and manufacturers, centred on patients and built for rapid development of personalized RNA medicines. What today is a scientific frontier will become clinical routine. For patients and their families, this means answers, options and real cures.

AI as a trusted partner for research in the Life Sciences

Florian Jug. In 25 years, AI will have matured. We will better understand its capabilities — but equally its limitations — and will have moved beyond today's inflated narratives about artificial general intelligence. Instead, we will distinguish more thoughtfully between general-purpose foundation models and domain-specific ones, each suited for different problems depending largely on the quality and quantity of available training data.

The past two decades have already shown what is possible: from rule-based image analysis and simple classifiers in the early 2000s, to today's models predicting protein structure or modelling cell behaviour based on different data modalities. This rapid evolution sets the stage for what comes next, but it can also give us a false sense that such acceleration will persist indefinitely, leading to inflated expectations.

Today, one of the most ambitious directions is the development of 'AI virtual cells' — comprehensive, data-driven models of cellular organization and dynamics. These initiatives are well funded and draw top talent, making them likely to become the proving ground for where the true utility — and limitations — of modern AI in the life sciences lies. Even if only partially successful, such efforts will enable us to pose fundamentally new questions in biology. They will illuminate critical challenges of multimodal data integration, prediction uncertainty and inherent limitations of generalizability — factors central to scientific discovery facilitated by AI.

Yet the biggest challenge may be a social one. As both data and models grow in complexity, cutting-edge discovery will increasingly require substantial investment and strong partnerships across experimental biology, AI, physics and medicine. No single laboratory will suffice, and transversal collaborations must be incentivized.

AI will not replace scientists, but it will become an indispensable partner in dealing with unfathomable amounts of rich, multimodal data — data to be mined to fuel our quest to understand the very fabric of life.

The coming age of mitochondria as architects of cell identity

Ana Victoria Lechuga-Vieco. In 25 years, mitochondrial biology will look completely different from what we know today. A major step forwards will be fully mapping how mitochondria specialize across different tissues and stages of development.

In the coming decades, I anticipate major advances in single-organelle omics and organelle-targeted genome editing technologies. These will include refined mitochondria-targeted base editors, synthetic import systems

for RNA and proteins, and tools to manipulate heteroplasmy levels or correct mutations in a cell-type-specific manner. Combined with spatial transcriptomics, these innovations will enable the precise dissection of how mitochondrial heterogeneity is established, maintained and disrupted in disease. Such insights will enhance our understanding of mitochondrial selection and quality control, enabling the development of targeted therapies that modulate these pathways. As a result, mitochondrial diseases, conditions once seen as enigmatic and untreatable, will become increasingly manageable through personalized therapeutic strategies. The understanding of tissue-specific mutation thresholds will make early diagnosis and precision interventions routine.

At the same time, synthetic mitochondrial engineering could become a reality. Mitochondria will be designed to enhance specific functions, whether it is energy production, redox balance or even immune modulation. Multiplexed reporter systems inserted into mitochondrial DNA will enable real-time monitoring of mitochondrial genome activity and stress signalling. As this knowledge continues to intersect with regenerative medicine, immunology and ageing research, it will fundamentally reshape how we understand health and disease by integrating knowledge of how mitochondria co-evolve with the nucleus and interact with other components of the cell.

By 2050, I envision a future where we no longer ask what mitochondria do for cells, but rather, what cell identities they help define.

RNA in full context

Raphaëlle Luisier. Hello RNA, my old friend, time has come to see you in full context.

Essential to life and central to disease, you have made headlines from COVID-19 to Nobel prizes.

Defying binary classification, you exist in biological superposition: coding and non-coding, catalytic and regulatory, structured and fluid.

In Verdi's words, you are a donna mobile: your identity emerges through reciprocal dynamics, shaped by context and reshaping it in return.

Like large language models for natural language, emerging AI tools are poised to reveal hidden patterns in RNA sequence. They can spotlight where patterns break, hinting at undiscovered conformations or modifications. These models will allow us to interpret a cell's RNA content as language: as a disordered book of expression, shaped by context, with each cell becoming a speaker of its own dialect, shifting across tissues, time and states.

Few molecules travel further than RNA across compartments, cells, organs and even individuals. Many RNAs and their related states remain undetected, lost to the limitations of current methods. Combining large language models with generative models and graph neural networks may help fill these gaps by modelling the landscape of RNA conformations, interactions and transitions across contexts. This modelling may expose a distinct grammar of regulation across scales, from cells to individuals.

RNA is indeed a living emergent grammar, irreducible to sequence alone. The real challenge for future AI tools is to predict what has yet to arise. However, as AI advances, its power will face limits: material, energetic, even epistemic. AI tools offer maps, not meaning. What remains limitless is the human capacity to think differently. Only by combining these tools with human memory, intuition and creative interpretation can we begin to grasp not just what RNA is, but what it may become.

Charting what is next for mitophagy

Julia Pagan. Mitochondrial degradation mechanisms, including mitophagy, safeguard against cellular dysfunction by removing damaged organelles and adjust mitochondrial networks for metabolic shifts during cell-state changes. Future priorities are to develop new tools for visualizing and quantifying degradation events in living systems, elucidate principles of mitochondrial selection and develop strategies that optimize mitochondrial quality across physiological states.

A major challenge is understanding how cells decide which and how many mitochondria to remove, and how this is coordinated with biogenesis and other quality control pathways. Within a single cell, mitochondria differ in mitochondrial DNA content, proteome composition, metabolic output and organelle interactions. Combined with cues from metabolic and stress responses, this heterogeneity influences removal through distinct mitophagy pathways, each recognizing distinct molecular signatures. Advances in super-resolution imaging, single-organelle omics and biosensor-based read outs will soon link specific molecular features to the selection of specific mitophagy pathways.

Another challenge is understanding how mitochondrial selection is regulated across tissues and coordinated with systemic cues such as nutrient availability, circadian rhythms, immune activity and physiological state. New technologies combining non-invasive imaging, circulating biomarkers and predictive modelling will measure degradation events in real time, map their tissue distribution and link them to metabolic turnover.

The next translational goal is to define the 'Goldilocks zone' for mitophagy in each tissue, disease stage or environmental context, a range where damaged mitochondria are removed without excessive depletion. This will require integrated approaches that both measure mitochondrial turnover in real time and allow controlled modulation of mitophagy. Biomarker-guided, context-specific therapies, whether enhancing mitophagy in neurodegeneration and metabolic disease or suppressing it in muscle wasting, could then progress to clinical application.

Looking ahead, synthetic organelles incorporating designer mitophagy receptors and engineered metabolic circuits could enable the targeted removal of damaged mitochondria and replenishment with healthy ones, transforming mitochondrial quality control in disease and biotechnology.

Emergent mechanisms of gene regulation in the nuclear context

Benjamin R. Sabari. Over the past 25 years, the field of transcription regulation has made remarkable progress in cataloguing the key factors that control gene expression (for example, transcription factors, cofactors, chromatin regulators and non-coding genomic elements). Advances in structural biology have yielded near-complete molecular views of these components in purified form, revealing intricate structure–function relationships. High-throughput sequencing has mapped regulatory elements genome wide, and microscopy has illuminated the dynamic behaviour of proteins and nucleic acids in living cells. Yet despite this progress, a central challenge remains: understanding how these components work together within the complex, crowded and heterogeneous environment of the nucleus, and the regulatory mechanisms that emerge from this complex interplay of many components.

The next 25 years will require a shift from studying mechanisms of isolated parts to uncovering regulatory mechanisms that emerge from nuclear context. How do differences in cell type, cell state or environment reshape the physical properties of the nucleus

in ways that influence transcription? How does local context at genomic loci modulate these regulatory processes?

Some emerging examples already hint at the power of context. Intrinsically disordered protein regions appear to organize transcriptional machinery through context-sensitive, multivalent interactions within condensates — behaviours that cannot be fully explained in dilute biochemical systems. Likewise, although transcription-regulating genomic elements are well annotated, we still lack a coherent model for how multiple enhancers, often separated by vast genomic distances, are coordinated in space and time to activate precise gene expression programmes.

Meeting this challenge will require both technological and conceptual breakthroughs. Super-resolution microscopy has already shown how protein behaviours in vivo diverge from cell-free behaviours. Looking forwards, integrating nanoscale imaging techniques such as MINFLUX and cryo-electron tomography with reconstituted systems that incorporate nuclear features will be essential. Computational frameworks — machine learning, spatial modelling and predictive simulations — will be equally crucial to interpret the complexity of the transcription environment.

Reconstituting cellular quality control pathways

Sichen (Susan) Shao. My laboratory seeks to elucidate molecular mechanisms of protein biosynthesis and quality control. For most of my career, my research has focused on 'housekeeping' processes carried out by conserved, ubiquitously expressed and usually abundant proteins that are essential for maintaining protein homeostasis in nearly all eukaryotic cells. Housekeeping proteins include chaperones and regulatory factors that interface with ribosomes during protein synthesis and components of the ubiquitin–proteasome system responsible for regulated protein degradation. A persistent mystery is why mutations or impairments in these broadly essential factors often lead to disease phenotypes that disproportionately affect certain cell types, such as specific neuronal or blood cell lineages. Generally, it remains unclear why particular cell types are selectively vulnerable to specific quality control defects and not others.

I believe the next 25 years will bring advances that enable more effective harnessing of comprehensive datasets to inform mechanistic studies. High-throughput functional genomics across diverse cell lines, combined with AI-aided data analysis and structural predictions, have already begun to clarify the functions of poorly understood factors in maintaining protein homeostasis and their interactions with cell-type-specific proteins. Improved quantitative proteomics and single-cell techniques are generating atlases with precise copy numbers of nearly every biological molecule in different cell types. Accurate knowledge of the relative stoichiometries of housekeeping factors and their substrates is essential for understanding the interplay between these pathways and how these balances vary across cell types.

The 'holy grail' of mechanistic understanding is to reconstitute a biological process entirely from purified factors. Future advances may enable us to reconstitute not only basic mechanisms but also their regulation in specialized contexts. Coupled with validations in improved induced pluripotent stem cell differentiation and organoid model systems, this will accelerate efforts to understand how protein homeostasis-associated diseases develop and identify better treatments.

Orchestrating necroptosis in cancer therapy

Liming Sun. Cancer's greatest trick is not avoiding death — it is dying quietly. Whereas apoptotic cells vanish without alerting immune surveillance, enabling tumour recurrence and therapeutic resistance, necroptosis screams. This 'loud' cell death floods tumour microenvironments with damage-associated molecular patterns, awakening dormant immune cells for both immediate clearance and long-term memory formation.

However, most cancers exhibit a peculiar paradox regarding the expression patterns of the serine–threonine-protein kinase RIPK3 and its substrate mixed lineage kinase domain-like protein (MLKL). Unlike classical kinase–substrate pairs, where kinases are broadly expressed and substrates tissue restricted, the necroptosis pathway inverts this pattern: RIPK3 expression is tightly restricted, whereas MLKL shows broad distribution. This pattern enables most cancers to avoid necroptosis induced by death receptors through RIPK3. This 'discordant state' is not simply an evolutionary accident — it is a therapeutic opportunity.

By 2050, direct therapeutic MLKL activation will bypass the requirement for RIPK3 entirely. Small-molecule activators, engineered peptides and modified oncolytic viruses will exploit ubiquitous MLKL expression in cancer cells independent of their RIPK3 status, converting immunologically cold tumours into inflamed, T cell-infiltrated lesions. The critical challenge lies not in proving MLKL activation efficacy, but in achieving precise temporal and spatial control. Emerging biomarkers will distinguish therapeutically beneficial necroptosis from pathological necrosis, restricting activation to early stage tumours where immune stimulation provides maximum benefit.

Necroptosis represents more than an alternative cytotoxicity mechanism — it embodies a paradigm where dying cells become immune educators. The next 25 years will witness necroptosis dominating through combination therapies pairing MLKL activation with checkpoint inhibitors, transforming dying tumour cells into endogenous vaccines. In this war, victory demands volume, not whispers, but molecular screams that rally immune armies.

Building models based on energy and matter

Jan J. Żylicz. My team studies how metabolism, epigenetics and signalling pathways coordinate early mammalian development. For me, the greatest unresolved challenge is both technical and conceptual. Technically, we lack methods that provide quantitative, multimodal measurements in space and time, that go beyond classical gene regulation. We do not understand how matter and energy flow through a developing organism, nor how these flows are molecularly linked to cell-state and cell-fate transitions. Conceptually, although it is clear that all modalities are coupled, we do not know how specificity is achieved. How can a global environmental change lead to a discrete cellular or organismal outcome?

I hope that in the next 25 years, we will harness advanced mass spectrometry for metabolomics and proteomics and integrate it with live imaging as well as DNA and RNA sequencing. We will be able to account not only for transcription, but also translation, metabolite dynamics and mechanical forces; all mapped across tissues and subcellular compartments. Such technology must be used beyond atlas generation exercises. It should be the cornerstone of the much-discussed 'virtual cell'. Indeed, quantitative multimodal datasets will enable the construction of in silico models of cells and even organisms — models that do not forget that life relies on basic principles of physics and chemistry.

The long-term ambition is to bridge the divide between chemistry and biology. If we can understand how matter and energy flow through a non-homeostatic system such as the developing embryo and how this flow interacts with cellular functions, we may finally answer fundamental questions such as 'How is complexity built?', 'How do cells self-organise?' and 'How is robustness and specificity achieved?'

Inspired by the success of protein structure predictions, the next frontier lies in the predictive modelling of cells and organisms based on matter and energy. These tools will not only describe biology but also generate new hypotheses.

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