

Book Review

The Cell Cycle and Development

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This book is the product of the recent Novartis Foundation Symposium by the same name. Rather than a mere collection of the manuscripts upon which symposium presentations were based, this volume remains faithful to the idea-sharing environment of the symposium by offering well-written summaries of 14 presentations, all in an engaging and eminently readable style. In addition, several pages of transcribed discussion follow each presentation, providing further insight into the topic and bringing into sharp relief the major questions remaining to be tackled in each individual field. The book also includes transcriptions of five general discussions, skillfully guided by symposium chair Paul Nurse, focusing on and comparing the more general questions raised by the presenters. The inclusion of transcribed discussion sections contributes enormously to the cohesion and readability of the book, providing a fascinating and holistic view of developmental control of the cell cycle on many levels, and in a variety of organisms.

This compilation investigates the developmental process from the point of view of the cell, exploring the interplay between the cell cycle and the developmental programs employed by various organisms. Key questions posed by Nurse in the symposium introduction include: How and why does the 'standard' cell cycle change in developing organisms, and what are the mechanisms that bring about these changes? How and why is the progression through the major cell cycle phases affected? What influences a cell's decision to stop proliferating and differentiate at a certain point in the developmental program, and how is differentiation achieved? These are all broad questions, and they are all addressed in a wide variety of organisms and discussed extensively by symposium participants. The individual topics addressed could be rather creatively put under the following general headings.

Cell cycle alteration and regulation in model organism development

This is a fundamental topic addressed by the symposium, and it receives extensive attention. The mechanisms that drive cell cycle transitions in the developing *Xenopus* are discussed in detail, with special attention paid to *Xenopus* oocyte maturation, and the development of checkpoint control of the cell cycle. The effect of DNA damage in the early embryo is considered; DNA damage has no effect on early *Xenopus* embryos, but when damaged embryos reach the onset of gastrulation, rapid and synchronous apoptosis occurs,

implying that the DNA damage checkpoint is activated at this stage.¹ The early mouse embryo also receives some attention, with focus on the cell cycle transitions undergone during the first mitotic cleavages.

Probably the most striking example of the degree to which the cell cycle can be altered to serve the changing needs of the developing organism is provided by *Drosophila* development; this system, as presented by Bruce Edgar, is representative of many of the fundamentals upon which this book is based, and so deserves some explanation.² During *Drosophila* embryonic development, cell cycle progression is mediated exclusively by cell-type-specific transcriptional enhancers. Such control makes sense during this developmental phase, since *Drosophila* embryonic cells undergo minimal growth between divisions. There is no need for cells to pause for growth following mitosis; the key event during this developmental phase is patterning, and this is quickly and effectively accomplished by allowing exclusive control of cell proliferation by pattern-inducing transcriptional enhancers. As development progresses to the larval phase, the developmental objective changes, and so too does the nature of the cell cycle. The major objective of *Drosophila* larval tissues is cell growth, rather than cell proliferation; larval cells undergo repeated rounds of endoreplication, an effect that may be designed to increase the total gene dosage in a given cell in an effort to support drastically increased cell size. In such cells, the cell cycle is controlled by nutrition; adequate nutrition triggers further rounds of DNA synthesis.³ In the undifferentiated larval imaginal cells, a combination of the two regulatory schemes mentioned above is observed. Imaginal disk cells in the developing larva must undergo both growth and patterning, and exhibit a 'classical' G1/S/G2/M cell cycle, with a growth-sensitive cell cycle checkpoint at the G1/S boundary and a patterning checkpoint at the G2/M boundary. The developmental program thereby neatly adjusts the cell cycle to promote patterning without growth, growth without patterning, or growth and patterning simultaneously, as each is required for proper development.⁴

Differentiation: how and when?

Closely related to cell cycle alteration during development is the topic of differentiation and the cessation of proliferation. Eventually, most developing cells stop proliferating and specialize; extensive attention is given to the mechanisms

by which the transition from proliferation to specialization is achieved and timed. The asymmetrical nature of many cell divisions is considered in the context of *Drosophila* neural progenitor cells, with focus on the protein interactions involved; one of the general discussions also focuses on the mechanisms of asymmetric cell division. Timing of differentiation is also considered in *Drosophila*, with special attention paid to the global vs cell-intrinsic nature of the timing mechanisms. Victor Ambros presents similar concepts in a *C. elegans* model, focusing on the tight control of postembryonic cell division by temporal regulation genes of the heterochronic gene pathway.

Also in this vein, the timing of cell cycle exit and proliferation in mammalian oligodendrocyte development is discussed by Martin Raff. This is a process notable for the autonomous control displayed by individual cells *in vitro*. Sister oligodendrocyte precursor cells plated in individual microwells differentiate at approximately the same time. Moreover, the differentiation mechanism does not count cell divisions as illustrated by the observation that in lower temperature conditions, cells divide more slowly, but differentiate after fewer divisions. It therefore appears that oligodendrocyte differentiation is controlled by a cell-intrinsic timing mechanism; the possible molecular basis for such a mechanism is discussed.⁵

Regulation of growth

A perennial topic of discussion is the relationship between growth and the cell cycle. Several of the general discussions focus on this topic, with key questions including: Can a cell sense its size? How does size influence cell cycle entry? Can a cell be too big? How is organ size, and even organism size, regulated? The role of growth factors in development is given some attention, particularly in the *Drosophila* imaginal disc.

The intriguing theories associated with imprinted gene expression are also considered in the developing mouse. The theory goes that, in mammalian fetuses, paternal copies of genes will encourage offspring to be greedy in an effort to maximize survival, while maternal genes will encourage frugality with maternal resources, to protect both the mother and the littermates. According to the theory, this sort of competition has given rise to gene imprinting, in which a gene's expression depends upon its parental origin; only paternal copies of certain genes are expressed, while only maternal copies of others are expressed. Indeed, presented findings show that, of the seven central control genes of fetal development, four are imprinted. Furthermore, knockout of paternally imprinted

genes leads to reduced fetus size, while knockout of maternally imprinted genes leads to increased fetus size, indicating that paternal genes are inducing growth, while maternal genes are slowing it down.⁶

Molecular underpinnings of cellular mechanisms

Asymmetric spindle positioning in the developing *C. elegans* embryo is considered in the context of the forces exerted by the cell to induce such asymmetry. A particularly interesting presentation by Kim Nasmyth also considers sister chromatid cohesion, both in the sense of initiation of cohesion following DNA synthesis and the release of cohesion during mitosis. The protein mechanism by which cohesion is initiated, possible relationships between cohesion and condensation, and the action of the Anaphase Promoting Complex, which induces the proteolytic cleavage that leads to chromatid separation at mitotic anaphase, are all considered in depth. This presentation also leaves the reader with a hint of intrigue, as another easily observable but as-yet-unknown molecular mechanism, which leads to separation of chromatid arms in condensed prometaphase chromosomes in higher eukaryotes, is known to act in the absence of the Anaphase Promoting Complex.⁷

All in all, this book is, by scientific standards at least, a page-turner. Encompassing a wide variety of techniques applied to many model organismal systems, this volume could equally serve a novice seeking a survey of the field, or an expert looking for information on the latest findings. The inclusion of discussion sections sheds welcome light on the fundamental questions addressed by each presentation, allowing the reader to keep a firm view of the forest while still appreciating the trees. The discussions tend to pose as many questions as they answer, a trait that could frustrate readers simply seeking concrete information, but providing more inquisitive readers with a welcome picture of what remains to be done in each area. The excellent organization and interesting content of this book make it recommended reading for anyone in the field.

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