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Review

Simple, realistic models of complex biological processes: Positive feedback and bistability in a cell fate switch and a cell cycle oscillator

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ABSTRACT

Here we review some of our work over the last decade on *Xenopus* oocyte maturation, a cell fate switch, and the *Xenopus* embryonic cell cycle, a highly dynamical process. Our approach has been to start with wiring diagrams for the regulatory networks that underpin the processes; carry out quantitative experiments to describe the response functions for individual legs of the networks; and then construct simple analytical models based on chemical kinetic theory and the graphical rate-balance formalism. These studies support the view that the all-or-none, irreversible nature of oocyte maturation arises from a saddle–node bifurcation in the regulatory system that drives the process, and that the clock-like oscillations of the embryo are built upon a hysteretic switch with two saddle–node bifurcations. We believe that this type of reductionistic systems biology holds great promise for understanding complicated biochemical processes in simpler terms.

1. Introduction

The South African clawed frog *Xenopus laevis* provides two powerful experimental systems for the study of the regulation of the universal M-phase trigger, CDK1: the maturation of *Xenopus* oocytes, and the rapid embryonic cell cycle [1]. Oocyte maturation is essentially a cell fate induction process, with the cell switching between two fairly static states, the G2-arrested immature oocyte and the M2-arrested mature oocyte. The embryonic cell cycle, in contrast, is dynamic. There are no steady states, and the embryo does not pause even in the presence of DNA-damaging agents. But both oocyte maturation and the embryonic cell cycle are well-suited to the detailed, quantitative biochemical dissection of the regulatory networks that drive these processes. And in both cases, our understanding of the processes has depended not only on experiments, but also on modeling studies that provide tests of whether our basic view of these processes is tenable or not, and on the theory of non-linear dynamics, which provides a more abstract and simpler view of the essence of this biology.

Here we review some of our work over the last decade on *Xenopus* oocyte maturation and the embryonic cell cycle. Our approach has been to start with wiring diagrams for the regulatory networks that underpin the processes; carry out quantitative experiments to describe the response functions for individual legs of the networks. And then construct simple analytical models based on chemical kinetic theory and the graphical rate-balance formalism. These studies support the view that the all-or-none, irreversible nature of oocyte maturation arises from a saddle–node bifurcation in the regulatory system that drives the process, and that the clock-like oscillations of the embryo are built upon a hysteretic switch with two saddle–node bifurcations. In a sense, oocyte maturation is as easy as falling off a log, and the embryonic cell cycle is a lot like falling off two logs over and over again.

2. Positive feedback, bistability, and oocyte maturation

2.1. Xenopus oocyte maturation as a cell fate switch

Xenopus oocytes begin life as cells not much larger than typical somatic cells (Fig. 1). They go through a normal G1-phase and a normal S-phase, and then carry out the early events of meiotic prophase: their homologous chromosomes pair up and undergo recombination. But instead of immediately proceeding to the first meiotic division, the oocyte enters a several-month-long growth phase. It grows to about the volume (1 μL) and protein content (25 μg) of approximately 400 000 NIH 3T3 cells, and then it stops. At this point the cell is technically still in meiotic prophase, but for

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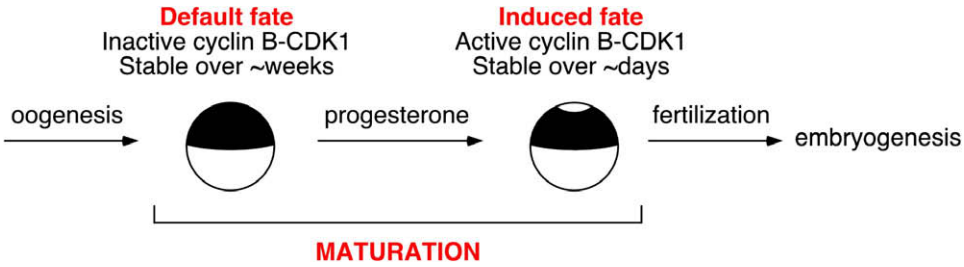

Fig. 1. *Xenopus* oocyte maturation as a switch between two cell fates.

practical purposes can be considered to be in G2-phase—transcription is taking place and the M-phase cyclins are present but locked in inactive complexes with CDK1—and its default fate is to remain arrested indefinitely in this state, with all its various opposing processes (protein synthesis/degradation, phosphorylation/dephosphorylation, anabolism/catabolism, etc.) in balance.

In response to gonadotropins released from the frog pituitary, the ovarian epithelial cells surrounding the oocyte release maturation-promoting hormones, which cause the immature oocyte to resume the process of meiosis. The classical maturation-inducing hormone is progesterone, and *Xenopus* oocytes possess both classical progesterone receptors [2–5] and seven-transmembrane G-protein-coupled progesterone receptors [6]. However, progesterone undergoes metabolism in the oocyte, and there is evidence that androgens and androgen receptors may ultimately mediate progesterone's effects [7]. Regardless of whether a progestin or an androgen is the ultimate trigger, the effects of progesterone on immature oocytes are striking. The oocyte leaves its G2-arrest state, carries out the first asymmetrical meiotic division, enters meiosis 2, and then arrests in metaphase of meiosis 2. This progression from the G2-arrest state to the meiosis 2-arrest state is termed maturation. After maturation the oocyte is ovulated, acquires a jelly coat, and is laid by the frog. It then drifts in the pond in this arrested state until either it is fertilized, which allows it to complete meiosis and commence embryogenesis, or it undergoes apoptosis.

In some respects oocyte maturation is an unusual example of a cell fate switch. Transcription is not absolutely required, and at least some aspects of maturation can even proceed in an enucleated oocyte [8]. However, in other respects it is absolutely typical: the cell responds to an external trigger by undergoing an all-or-none, irreversible change in its appearance, its biochemical state, and its developmental potential.

2.2. Mos, p42 MAPK, and CDK1 activation

Although many details remain to be worked out, in broad outline the signaling network that mediates progesterone-induced oocyte maturation is well-understood (Fig. 2). Progesterone stimulates the translation of the Mos oncoprotein, a MAP kinase kinase kinase (MAPKKK). Active Mos phosphorylates and activates the MAPKK MEK1, which then phosphorylates and activates ERK2 (which in *Xenopus* is often called p42 MAPK). Inhibitors of these MAPK cascade proteins inhibit oocyte maturation, and activated forms of the proteins can initiate maturation in the absence of progesterone.[1] p42 MAPK activation then brings about the dephosphorylation and activation of cyclin B-CDK1 complexes (sometimes termed "latent MPF", for latent maturation-promoting

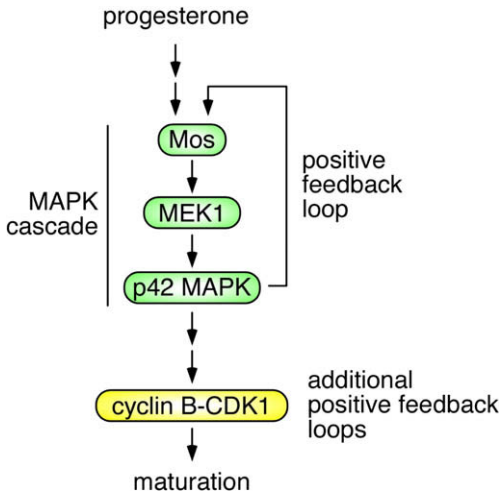

Fig. 2. Signal transduction pathways involved in *Xenopus* oocyte maturation.

factor, or "pre-MPF"). Activated cyclin B-CDK1 complexes then cause the oocyte to re-enter meiotic M-phase.

Cyclin–CDK complexes are thought to function as near perfect switches at the level of the individual complex: for example, a fully activated cyclin A-CDK2 complex is approximately 10^9-fold more active than an "inactive" CDK2 monomer [9]. But an oocyte possesses $\sim 10^{10}$ cyclin B-CDK1 complexes, meaning that even if an individual complex is perfectly all-or-none in its activity state, the population of cyclin B-CDK1 complexes could, in principle, settle into a nearly continuous range of graded activities. This raises the question of how the all-or-none character of oocyte maturation arises. Is the process all-or-none at the level of p42 MAPK activation and/or CDK1 activation? And how do these reversible activation processes culminate in an irreversible cell fate change?

2.3. The all-or-none, irreversible response depends upon positive feedback

Analysis of individual oocytes treated with various concentrations of progesterone demonstrated that the steady-state response of the oocyte's MAPK cascade is essentially all-or-none (Fig. 3). At intermediate concentrations of progesterone, individual oocytes were found to have either all of their p42 MAPK non-phosphorylated or all of it phosphorylated. Thus, somewhere between the progesterone receptor and the bottom of the MAPK cascade, a graded "analog" progesterone stimulus is converted to a "digital" MAPK response. Moreover, the steady-state response of MAPK to microinjected Mos is also all-or-none [10]. This demonstrates that the MAPK cascade can generate an all-or-none response, not simply propagate one. A plausible mechanism for the generation of the all-or-none response was suggested by the discovery that, in oocytes, p42 MAPK and CDK1 are organized in positive feedback

[1] There is some disagreement on whether the Mos/MEK/MAPK cascade is required or dispensable for progesterone-induced oocyte maturation. See for example, Refs. [9–11].