Signalling pathways in oocyte meiotic maturation

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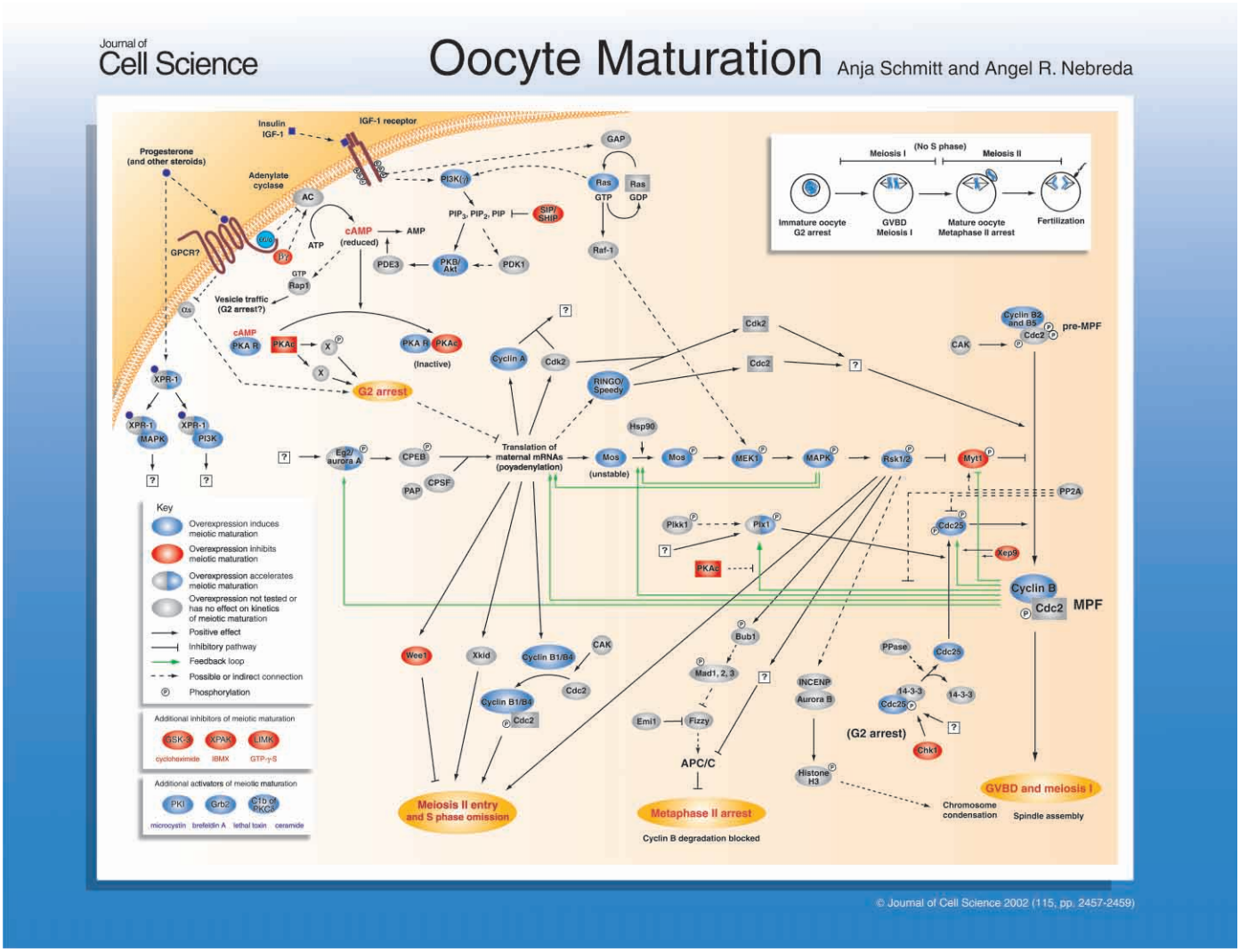
Immature oocytes become fertilisable eggs through a process called meiotic maturation, which is often induced by specific hormones. Oocyte maturation involves the activation of various signal transduction pathways that converge to activate maturation-promoting factor (MPF); this is a key activity that catalyses entry into M-phase of meiosis I and meiosis II. Whereas the function of MPF in promoting oocyte maturation is ubiquitous, there are species-dependent differences in the signalling pathways leading to MPF activation. The poster is based mainly on the signalling pathways elucidated in oocytes of the African clawed frog *Xenopus laevis*, which is probably the most intensively studied model system for meiotic maturation. Important differences between oocytes from *Xenopus* and other organisms are discussed below. Further details and primary references can be found in several recent reviews (Abrieu et al., 2001; Ferrell, 1999; Karaiskou et al., 2001; Maller et al., 2001; Nebreda and Ferby, 2000; Yamashita et al., 2000).

Fully grown oocytes are arrested at the first meiotic prophase. The hallmarks of meiotic maturation in vertebrate oocytes are (1) resumption of meiosis I which includes germinal vesicle breakdown (GVBD), chromosome condensation and spindle formation, (2) the transition between meiosis I and meiosis II, including inhibition of S-phase and (3) arrest in metaphase II because of cytostatic factor (CSF) activity. Meiosis II is completed after fertilisation of the mature oocyte (or egg). By contrast, oocytes of many invertebrates proceed during maturation only to metaphase of meiosis I, which is when they are fertilised.

In *Xenopus* oocytes, maturation is thought to be initiated by the steroid hormone progesterone, which is synthesised and released by follicular



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cells surrounding the oocyte. However, maturation can also be induced by other steroid hormones, and androgen rather than progesterone has recently been proposed to be the primary steroid produced in *Xenopus* ovaries. Insulin and insulin-like growth factor-1 are also able to induce oocyte maturation in vitro probably via an IGF-1 receptor. It is not yet clear how many of the signalling molecules probably involved in insulin-induced oocyte maturation (such as Ras, Raf-1, PI3K, PDK1 and PKB) are also implicated in progesterone-induced maturation. Overexpression of signalling molecules may trigger activation of signal transduction pathways that result in meiotic maturation without playing a role themselves in the progesterone-triggered process.

There is some evidence that the progesterone receptor in *Xenopus* oocytes is a membrane-bound receptor, possibly coupled to heterotrimeric G-proteins, which inhibit adenylate cyclase. However, the function of the heteromeric G-proteins in meiotic maturation is not completely understood. Overexpression of activated $G_i\alpha$- and $G_o\alpha$-subunits can induce meiotic maturation, whereas the $G_s\alpha$- and, more recently, the $G\beta\gamma$-subunits have been proposed to have roles in the G2 arrest of *Xenopus* oocytes. By contrast, in starfish oocytes, the $G\beta\gamma$-subunit activates meiotic maturation, which may be mediated by PI3K activation. Recently, an intracellular *Xenopus* progesterone receptor (XPR-1) has been described that is homologous to the ‘classic’ mammalian progesterone receptor and can interact with both PI3K and MAPK. It remains to be elucidated whether XPR-1 is the only progesterone receptor in the oocytes and how it functions.

One of the earliest biochemical changes detected in frog oocytes after progesterone stimulation is a decrease in the concentration of cAMP, which has also been described in other species including mouse, rat and fish. Consistently, the cAMP-dependent protein kinase (PKA) is a potent inhibitor of meiotic maturation, an effect that does not require its catalytic activity, and inhibition of PKA alone is sufficient to induce *Xenopus* oocyte maturation. By contrast, maturing oocytes from pig, sheep and rabbit exhibit a transient increase rather than a decrease in cAMP levels, and treatments that increase cAMP levels can induce oocyte maturation in jellyfish.

An important feature of meiotic maturation in *Xenopus* oocytes is the translation of maternal mRNAs, which usually correlates with their polyadenylation. These oocytes are unable to undergo GVBD in the presence of protein synthesis inhibitors, indicating that newly synthesised (or short lived) proteins are necessary for the initiation of meiotic maturation. Cow, goat, pig and sheep oocytes are also unable to undergo GVBD in the presence of protein synthesis inhibitors. By contrast, mouse oocytes can undergo GVBD in the presence of protein synthesis inhibitors, and newly synthesized proteins are required only for the completion of meiosis after GVBD.

The first maternal mRNA shown to be important for *Xenopus* oocyte maturation encoded the protein kinase Mos, an oocyte-specific MAPK kinase kinase that leads to the activation of the protein kinase p90Rsk, which in turn can phosphorylate and inhibit the Cdc2 inhibitory kinase Myt1. In starfish oocytes, however, Myt1 is inhibited by the protein kinase PKB/Akt. A role for PKB in *Xenopus* oocyte maturation remains to be demonstrated, although overexpression of PKB can trigger maturation in *Xenopus* oocytes. In mouse oocytes, Mos has been proposed to inhibit a MAP phosphatase in addition to activating the MAPK kinase MEK1.

The role of MAPK in meiotic maturation varies among different species. In mammalian oocytes, MAPK is activated during maturation but oocytes from c-mos knock-out mice, in which MAPK is not activated, can undergo GVBD. *Xenopus* oocytes can also undergo GVBD in the absence of MAPK activation, although with delayed kinetics. In maturing starfish oocytes, MAPK is activated only after MPF activation and GVBD. Moreover, these oocytes do not arrest at metaphase II but proceed to interphase and contain high levels of MAPK activity. Therefore, in contrast with amphibian and fish oocytes, MAPK is related neither to GVBD nor to metaphase arrest in starfish oocytes.

Other maternal mRNAs that are translated during *Xenopus* oocyte maturation encode cyclins B1 and B4 and the chromokinesin Xkid. These proteins are all dispensable for meiosis I entry but play essential roles in the progression from meiosis I to meiosis II. RINGO/Speedy is a Cdc2 and Cdk2 activator, whose accumulation seems to be required for progesterone-induced oocyte maturation.

In *Xenopus* oocytes, there is a stock of inactive Cdc2–cyclin B complexes named pre-MPF, which are activated by dephosphorylation of Cdc2 on Tyr-15 (and probably also Thr-14). The phosphatase responsible for this dephosphorylation is most probably Cdc25, which can be regulated by both phosphorylation and subcellular localization. Plx1 is a possible activator of Cdc25, but it is not clear how this signalling pathway may be initially stimulated. In immature oocytes of fish and other amphibians, except *Xenopus*, only monomeric Cdc2 but not pre-MPF is present, so that cyclin B needs to be synthesised from maternal mRNAs for GVBD.

The protein kinase Rsk seems to play important roles during the meiotic cell cycle. Rsk participates in meiosis I entry (probably via inhibition of Myt1) and may also downregulate the S-phase between meiosis I and II, perhaps through the re-activation of MPF. In addition, Rsk contributes to metaphase II arrest, by activation of either Bub1 or an as yet unkown CSF pathway, which inhibits the anaphase-promoting complex (APC/C). The MAPK/Rsk pathway is also necessary for the activation of a histone H3 kinase, possibly aurora B, during oocyte maturation.

An important feature of meiotic maturation is an extensive network of feedback signalling (mostly downstream of MPF activation), which is responsible for the generation of an all-or-none response ensuring that the oocyte completes meiotic progression. These feedback mechanisms often make it

difficult to determine the order of events in a signalling cascade, since a small level of MPF activity is sufficient to activate most of the pathways involved in oocyte maturation.

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