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This Week's Citation Classic®

Masui Y & Markert C L. Cytoplasmic control of nuclear behavior during meiotic maturation of frog oocytes. *J. Exp. Zool.* 177:129-45, 1971.
[Department of Biology, Yale University, New Haven, CT]

The discovery of maturation promoting factor (MPF) and cytostatic factor (CSF) in *Rana pipiens* oocytes is reported. When oocytes mature, MPF is autocatalytically activated to drive the chromosome cycle to metaphase, where it is arrested by CSF. Both factors disappear at fertilization. All these processes require no nuclear activities. [The *SCI*® indicates that this paper has been cited in over 290 publications.]

Yoshio Masui
Ramsay Wright Zoological Laboratories
Department of Zoology
University of Toronto
Toronto, Ontario M5S 1A1
Canada

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In 1966 I visited Clement L. Markert at Yale University to learn how to approach the problem of differential gene activation through isozyme analysis of developing embryos. A year later, when I finished a study of penguin LDH isozymes, Markert suggested that I should start something else that I was interested in. By that time, I had realized that cell differentiation was a formidable problem for molecular biology of the 1960s, and I wanted to study much simpler cell changes in better-defined systems.

I had previously trained as an experimental morphologist and had studied (for my PhD) embryonic induction. Therefore, I was interested in the possibility of developing an *entwicklungsmechanik* of subcellular processes. When I learned about the work by T.A. Dettlaff and her associates in the USSR on amphibian oocyte maturation,[1] I thought that this was it and immediately repeated their work. However, I was unable to reproduce some of their results and corrected their conclusion as follows: the pituitary hormone does not act on the oocyte as they thought; it is rather a progesteronelike hormone secreted by follicle cells responding to the pituitary hormone that induces oocytes to resume meiosis and initiate maturation.[2] However, when progesterone was injected into oocytes, it had no effect.[3] Therefore, we proposed a hypothesis in the cited paper: We stated that "external stimuli apparently act primarily on the cortical cytoplasm to generate the factors which secondarily control nuclear behavior" (p. 130); and we presented evidence for this hypothesis as summarized in the abstract above.

All efforts during the following years, however, failed to elucidate molecular characteristics of these factors, until I moved to the University of Toronto in 1969 and developed a new method to prepare oocyte cytosols containing active factors. Thus, in 1976 we succeeded for the first time in partial characterization of maturation promoting factor (MPF),[4] and in 1984 we developed a cell-free system to observe MPF activity *in vitro*.[5] Recently, important roles of MPF in cell cycle control have been widely recognized, and application of gene technology to its analysis is coming into sight.[6] Coincidentally, our cited paper appears to be gaining popularity.

Once, Markert suggested to me that I should choose a project that I could continue in Japan, because I was supposed to go back to that country, which was very poor back then, and spend the rest of my life with little funding to carry out expensive projects. Following his suggestion, I chose this project. Retrospectively, this was the right choice. Although I did not go back to Japan, I had to continue my research for a long time with a small grant, which was usually all that junior researchers working outside of medicine could receive in Canada. Listening to my complaints about the situation, Markert said: "I know it is difficult for your kind of research to attract money. But, don't give up. Your research is important." I believe that, without these words, my research would have perished under the strong pressure of international competition.

1. **Dettlaff T A, Nikitina L A & Stroeva O G.** The role of the germinal vesicle in oöcyte maturation in anurans as revealed by the removal and transplantation of nuclei. *J. Embryol. Exp. Morphol.* 12:851-72, 1964. (Cited 90 times.)
2. **Masui Y.** Relative roles of the pituitary, follicle cells, and progesterone in the induction of oöcyte maturation in *Rana pipiens*. *J. Exp. Zool.* 166:365-76, 1967. (Cited 200 times.)
3. **Smith L D & Ecker R E.** Role of oöcyte nucleus in physiological maturation in *Rana pipiens*. *Develop. Biol.* 19:281-309, 1969. (Cited 150 times.)
4. **Wasserman W J & Masui Y.** A cytoplasmic factor promoting oocyte maturation: its extraction and preliminary characterization. *Science* 191:1266-8, 1976. (Cited 90 times.)
5. **Lohka M J & Masui Y.** Effects of Ca^{2+} ions on the formation of metaphase chromosomes and sperm pronuclei in cell-free preparations from unactivated *Rana pipiens* eggs. *Develop. Biol.* 103:434-42, 1984. (Cited 15 times.)
6. **Robertson M.** Molecular associations and conceptual connections. *Nature* 334:100-2, 1988.