Developmental Control of Human Preimplantation Embryos: A Comparative Approach

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The period for which oocyte-derived factors are engaged in the control of human embryonic development involves at least the first four cell cycles after fertilization. The maternal-embryonic transition in human 8- to 16-cell embryos is a relatively vulnerable process, the failure of which entails developmental arrest of the given blastomere. The very early cellular differentiative events in human embryos, including blastomere surface polarization and segregation of the inner cell mass and trophectoderm cell lineages, appear to be dependent largely on the maternal genetic program. However, the embryonic genome is required for the formation of the blastocyst cavity, which is necessary to allow further differentiation of the first two embryonic tissues. Blastomeres with major developmental defects are removed by fragmentation and their loss is compensated by proliferation of remaining normal blastomeres. This mechanism is also mainly responsible for the regulation of ploidy through elimination of aneuploid blastomeres. The data presented suggest that embryos of individual mammalian species may differ in the timing of relevant developmental changes at the cellular and molecular levels. This should be taken into account when findings obtained on embryos of one species are used to anticipate the behavior of embryos of another species under identical conditions.

KEY WORDS: developmental control; human preimplantation embryo; embryonic genome activation; cell lineage segregation; regulation of ploidy.

INTRODUCTION

The current developments in the field of human in vitro fertilization (IVF) and embryo transfer demonstrate that this method has depassed its "classical" sphere of application. Originally conceived as a method of treating female sterility due to anatomically or functionally defective fallopian tubes, IVF has broadened its scope during the past several years and has become a recognized alternative in the treatment of female and male infertility of various etiologies, including endometriosis, spermatozoal disorders, abnormal immunological responses to gametes, and a relatively great group of patients suffering from infertility of unknown causes. The actual progress in the fields of ovarian cycle monitoring, gamete and embryo culture, cryopreservation, and micromanipulation has also contributed to the overall enlargement of the application scale of IVF in human reproductive medicine. With the use of this technological progress the first steps have been made in advancing programs of oocyte and embryo donation, and studies aimed at utilizing preimplantation human embryos for early genetic diagnosis are now under way. In the latter application IVF will, for the first time, leave the domain of infertility treatment to become a tool of wider medical significance. All these new developments are covered by a complex of clinical and research activities for which the term "human reproductive technologies" is the most appropriate expression.

Facing this qualitatively new situation, workers in human IVF will obviously feel a growing need for getting a deeper insight into the mechanisms governing the early development of the human embryo. This information is necessary to avoid the risk of pure empiricism. A cardinal question which must be posed by the student of early human embryology is how to obtain information about the control of human preimplantation development. Since the access to "supernumerary" embryos from human IVF...
programs and the possibilities of their use for experimentation are limited, another question arises: how to use data obtained on animal embryos to fill the gaps in our understanding of analogous processes in humans.

In this article I summarize the actual knowledge of the developmental mechanisms in human preimplantation embryos and confront it with data available for embryos of other mammalian species. The aim of this approach is to replace the mechanistic reasoning, anticipating a similar behavior of corresponding developmental stages of different species, with a more physiologically founded strategy taking into account both interspecies similarities and interspecies differences in the character and timing of basic cellular and molecular events during mammalian preimplantation development.

ACTIVATION OF THE EMBRYONIC GENOME

It is generally accepted that differential gene activity is a major (although not the only) mechanism controlling differentiation and developmental processes in living cells. A unique feature of early animal embryos is the coexistence of gene products originating from two genomic sources. The products of oocyte genome are transmitted to the early embryo in the form of a variety of metabolites, enzymes and other proteins, and biological membranes and, last but not least, a set of RNA molecules among which all major classes of RNA are represented. The embryonic genome, resulting from integration of the oocyte genome and that of the fertilizing spermatozoon, is a second source contributing the information necessary for the control of developmental processes. While, in general, the earliest postfertilization stages are largely under oocyte (maternal) control, this function is later progressively assumed by the embryonic genome, the activation of which, however, begins at different embryonic stages, depending on the species (for review see Ref. 1).

As for mammals, the genetic control of preimplantation embryonic development has been studied most extensively in the mouse. During the first cell cycle after fertilization (pronuclear stage) the mouse embryo shows little detectable RNA synthesis (2,3) and its development is not affected either by physical enucleation (4) or by using transcriptional inhibitors (5,6). A slight synthesis of polyadenylated RNA (presumably mRNA) has been detected only at the late one-cell stage (7). Beginning with the two-cell stage, the mouse embryo shows an intense and gradually increasing incorporation of labeled precursors into all qualitatively different species of RNA (3,8-11). Coincidentally with the activation of embryonic genome transcription, the transition of the control of main developmental processes from maternally derived transcripts to embryonic genome-derived transcripts begins at the two-cell stage of mouse development, when the embryo also becomes more sensitive to physical enucleation or transcriptional inhibitors (for reviews see Refs. 6, 12, and 13). It is also the two-cell stage at which the expression of paternal genome has been first documented in the mouse embryo using both biochemical (14) and morphologic (15) markers, even though there is some recent evidence suggesting the contribution of the paternal genome to early developmental mechanisms as early as the late one-cell stage of mouse development (16). Once the major outburst of the embryonic transcriptional activity has occurred in the two-cell mouse embryo, maternal RNA becomes rapidly degraded, as reflected by a sharp fall in the total RNA (17), marked reduction of the total poly(A) content (3,11), dramatic decline in the content of poly(A)+ RNA labeled during oocyte growth (18), and noticeable decrease in the number of ribosomes (3). After the mid two-cell stage, there are no maternal effects that could be clearly ascribed to the persistence of active maternal RNA (12). This does not imply, however, that the switch from the maternal to the embryonic genome function in the mouse embryo is a rapid one-step event. On the contrary, oocyte gene products apparently persist in the embryo cytoplasm long after the disappearance of maternal RNA. For instance, the oocyte-coded form of the enzyme glucose phosphate isomerase lasts in the mouse embryo until at least 5.5 days postcoitum, while both the maternally and the paternally derived alleles for this enzyme are first expressed between 2.5 and 3.5 days postcoitum (19).

With regard to the relative availability of data about the genetic control of early mouse embryogenesis, information obtained on the mouse model was often extrapolated to other mammalian species, despite the lack of sufficient evidence permitting such a generalization. In fact, among the studies performed on other mammalian species, many pointed out conspicuous differences. In the rabbit embryo, for example, there is a considerable delay in the activation of embryonic rRNA production,