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Darwin's Gemmules and Development

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ABSTRACT Nowadays, Darwin's pangenesis hypothesis and his gemmule idea are considered to have been completely denied. However, the pangenesis hypothesis constituted, whereof we now often forget, an integral and essential part of Darwinism. There offered a hypothesis that probably to the certain period of embryonic development yet unidentified substances of specialized cells, tissues and organs of foetus, but not those of maternal organism, are cumulated in oocyte cytoplasms. These substances, so-called Darwin's gemmules (DGs), take part in determination and differentiation of a future embryo's cells. The approaches of experimental detection of DGs are also discussed.

INTRODUCTION

The germ cell lineage carries the potential for both totipotency and immortality. It forms the fragile link between one generation and the next, and so is of central importance for the survival and evolution of living organisms (McLaren 1998).

Embryogenesis – how the tissues and organs of the developing embryo take their miraculous forms – is currently explained in terms of genes, hormones and chemical gradients. Although, we have solved the Human Genome, we still do not understand how embryonic tissues and organs are physically constructed with three-dimensional forms optimally designed to carry out their specialized functions (Ingber 2006).

Development is the function of genes in embryonic cells. Determination precedes differentiation. Determination means commitment; the final realization of this commitment is differentiation. When a cell achieves its determined fate it is said to have differentiated. Differentiation is the prime problem of developmental biology (Purves et al. 1997). Differentiation is not just a matter of genes and cortex and cytoplasm interacting with each other but also of the genes of one generation controlling those of the next generation during the very early development (Moor 1986).

Genes control the cellular synthesis and through them cell structure and function. How are differential patterns of gene activity instituted? Why should the cells of an organism produced by repeated cell divisions and containing identical genetic material show the range of diversity, which typifies higher multicellular organism? The answer is far from clear but must involve the induction and repression of genes.

The main genetic problem of embryonic development is differentiation. At present time, theories of differentiation at gene level can be considered refuted. Indeed, genomes of all cells are identical. As a rule, control of differentiation is carried out on a transcriptional level: differentiated cells produce various numbers of mRNAs. Regulation on the other levels, less connected to a primary activity of genes, is also possible. However, the exact mechanism of such control of higher eukaryotes is not determined.

Cytoplasmic control is of enormous importance in early development. Evidence for the importance of the cytoplasm accumulated in the late 19th century. Numerous examples are now known of the effects of the cytoplasm on the nucleus. Classic experiments of Hörstadius and Spemann established that the unequal distribution of materials in the egg cytoplasm plays a role in directing embryonic development. They were named 'cytoplasmic determinants' (Purves et al. 1997). However, those hypothetical cytoplasmic determinants are not identified yet and still elude sophisticated methods and machines of science.

Now, Darwin's hypothesis of pangenesis and his gemmule idea are considered as completely denied. Apparently, modern biologists who communicate amongst each other in the language of genetics and molecular biology look at a colleague who thinks on a gemmule level as a

hopelessly retrograde person. Taking the risk of provoking irony, nevertheless, I will apply my considerations of not only gemmules, but also probable places of their detection and ways of search.

WHY DARWIN'S GEMMULES?

As far as it is known, the main theses of Darwin's pangenesis hypothesis consist of the following: a) germ cells, from which a new organism is developing, are generated as a result of vital activity of maternal organism; b) individual signs of the whole organism are represented in each germ cell by certain material particles – gemmules (these particles are able to feed and breed by division, and during the cell division they are distributed to daughter cells); c) organism's cells at all developmental stages detach similar gemmules and deliver them to germ cells; d) gemmules transmit to germ cells the signs, which were acquired by respective original cells in the process of their development; e) changes of either one or another organ under the influence of external stimuli are immediately reflected on gemmules and through them on germ cells. It also should be underlined that the hypothesis of pangenesis constituted an integral and essential part of Darwinism, whereof we now often forget.

The main point of my hypothesis is that probably to the certain period of embryonic development yet unidentified substances of specialized cells, tissues and organs of foetus, not maternal organism, are cumulated in mature oocyte cytoplasms. These substances, which I conditionally call Darwin's gemmules (DGs), will take part in determination and differentiation of a future embryo's cells.

My hypothesis, keeping the fundamental idea of Darwin, just specifies that:

a) DGs are formed not in the process of vital activity of maternal organism, but at the stage of its embryonic development even in a mother's womb.
b) As far as it is known, from all cells of foetus only oocytes cease mitotic divisions and stay in the same condition before sexual maturity. That is why it can be expected that substances, including DGs, produced by foetus's specialized cells, tissues and organs, could be conserved in oocyte cytoplasms. In mature male germ cells cytoplasmic material is practically absent; thereby, the presence of DGs in those cells is not expected.
c) The Sertoli cells are thought to provide mechanical support, protection and nourishment during maturation of spermatozoa. All nutrients, oxygen and waste substances exchanged between the developing gametes and the blood vessels surrounding the tubules pass through the Sertoli cells. Unlike the production of spermatozoa in males, which only begins at puberty, the production of ova in females begins before birth and is completed only after fertilization. During foetal development primordial germ cells (PGCs) undergo repetitive mitotic division and produce many larger cells – oogonia. These undergo mitosis and form primary oocytes, which remain at prophase of this stage until just before ovulation. Primary oocytes are enclosed by a layer cells and form structure known as primordial follicles. The role of primordial follicles is apparently the same as of Sertoli cells. However, I assume that unlike Sertoli cells the dense layer of follicle cells has one more important function: they prevent oocyte cytoplasm penetration by the products of vital activity of specialized cells, tissues and organs of both foetus's and maternal organism. In other words, starting with meiosis prophase I the flux of DGs in oocyte cytoplasm ceases, as since that time they have been isolated from the influence of other cells by a permanent layer of primordial follicles.

All that creates a unique situation: oocytes become the only cells in a body of multicellular organism where hypothetical DGs of foetus could be conserved. If so, then DGs could be represented as one of the forms of cytoplasmic determinants, switching on genes at different stages of embryogenesis. With the help of DGs different genes are activated in cells from different layers (ectoderm, mesoderm, and endoderm), so that different gene products are formed. That is why it is assumed that DGs are already present in the unfertilized egg cytoplasm and these cytoplasmic determinants play a role in directing embryonic development.

Thereby, only oocytes can conserve some quantity of DGs from specialized cells, tissues and organs of foetus. This circumstance is conceived to be especially important for the

following reasons: a) if DGs were cumulated from all types of highly specialized cells of maternal organism, and a human being has 260 ones (Lima-de-Faria 1983), then embryogenesis would be an extremely confused and uncontrollable process; b) if DGs were cumulated in oocytes during the whole embryonic and reproductive period, then this, besides the inheritance of deleterious mutations in somatic cells, would lead to (to the delight of lamarkists) the inheritance of other acquired characters of maternal organism.

HOW TO DETECT DARWIN'S GEMMULES?

It has to be admitted that nobody using the newest methods of cellular biology looked purposefully for DGs, for after the rediscovery of Mendel's laws at the beginning of the 20th century searching for DGs is considered to be a useless venture *a priori*.

The proposing scheme of experimental detection of DGs is based on peculiarities of the female germ cell development, and it depends on a selected experiment subject. The best-known gametogenesis is one of a human being and a mouse.

As far as it is known, PGCs of a human being leave the yolk sac on the 27th day after fertilization and migrate to the genital ridge. On the 46th day of pregnancy, gonads undergo the sex differentiation and become either ovaries or testicles (Ibraimov 2008). After the sex differentiation, following the mitotic division a fast increase of a number of ovary stem cells occurs. Women before the 3rd month of pregnancy are noted to have only mitotic divisions. Then, the first meiotic divisions become able to be seen. The first pachytenes and diplotenes are observed with a seven-month foetus. Then, meiosis slows down, nuclear membrane is produced, nucleolus develops and cells enter "the resting phase", dictyotene. The cells surrounding oocyte function as feeding; later they will originate a follicle in which the oocyte is enclosed (see above). Oogonia having existed more than seven months undergo degeneration. After birth, all stem cells are generally utilized: oogonia turn into oocytes or degenerate. Approximately $2x10^6$ of these follicles exist in the foetal female just before birth but only about 450 ever develop into secondary oocytes, which are released from the ovary during the oestrous cycle. Meiosis comes to the end only after fertilization (Vogel and Motulsky 1986).

Human being oocytes are completely developed already at a late embryonic stage. The fact that the only one of four cells develops into a mature oocyte, and three polar bodies have almost no cytoplasm, gives an opportunity to that oocyte to transmit to a new zygote a complete set of cytoplasmic components, such as mitochondria and mRNAs. And I conceive that besides other oocyte cytoplasmic components there can be DGs as well. Moreover, the next assumption is highly probable too: the large size of oocytes in comparison with other cells may have been caused by additional accumulation of cytoplasmic materials at the expense of degenerated oogonia. These circumstances could have a deep biological sense in the meaning of their bringing DG concentration increase in oocyte cytoplasms being necessary for embryogenesis.

Thereby, the peculiarities of oogenesis suggest a scheme of experiments aimed at detecting DGs in a human being. We suppose that the most appropriate method of the DG detection is the use of existing methods of the nucleus transplantation. Taking this aim into account, it is suggested withdrawing nuclei from fertilized eggs (or from first blastomeres) and transferring them into enucleated oocytes, oogonia and PGCs. If our idea is right, then cytoplasms of oocytes, oogonia and PGCs will have to differ from each other in quantitative and qualitative DG composition, i.e. their determining potentials will have to diminish in the following direction: oocytes → oogonia → PGCs. In other words, morphogenetic effects of cytoplasmic determinants must be determined by the stage of foetus's or embryo's development, from where the cells for nucleus transplantation have been extracted.

Nevertheless, the most appropriate subjects for such experiments mice can happen to be, all stages of germ cell development and embryogenesis of which are scheduled literally day by day. Thus, e.g. mouse PGCs are first recognizable in the posterior region of the extraembryonic mesoderm at around 7.25 days post coitus (dpc) (Chiquoine 1954; Ginsburg et al. 1990). From around 8.5 dpc, PGCs migrate into the embryonic mesoderm, through the hindgut endoderm and along the dorsal mesentery, and

finally into the genital ridge at 10.5 – 11.5 dpc. PGCs continue to proliferate mitotically during the migration and after arrival at the genital ridge until 12.5 – 13.5 dpc. At 12.5 dpc, developing gonads show the first signs of sexual dimorphism with testicular cord formation in the males. In the ovary, they enter into meiosis and become oocytes, which are arrested in the prophase of the first meiotic division. In the testis, PGCs are mitotically arrested in the G1/G0 phase and become prospermatogonia, which later restart mitosis as spermatogonia and produce meiotic spermatocytes postnatally (Hilscher et al. 1974). Consequently, to detect a mouse DGs withdraw PGCs at the moment they become recognizable in the posterior region of the extraembryonic mesoderm, i.e. at around 7.25 dpc, then at 10.5 – 11.5 dpc, when PGCs enter the genital ridge, and finally at 12.5 dpc, when PGCs arrive at the genital ridge and developing the first signs of sexual dimorphism and become oocytes, which are arrested in the prophase of the first meiotic division.

If it may seem to anyone that the concentration of DGs in the cytoplasm of a fertilized egg to be too low to determine the development of embryo's numerous cells, then it is to be remembered several well-known examples: a) in an average animal cell there are approximately 3×10^{13} macromolecules (Albrecht-Buehler 1990); b) the number of hormones of an adrenal glands, being produced throughout the whole life of a human being, does not exceed one gram, and their effective concentration in blood makes up 1: 1-2 billions; c) one single molecule may be enough to convey the massage. The antennae of an adult silkworm are able to recognize and react to a single pheromone molecule (Schneider 1969).

DISCUSSION

To defend the suggested idea it is necessary to cite here several well-known general biological theses.

After removal of the surrounding follicle cells, the mature oocyte can be fertilized and the resulting embryo transferred to the uterus, where it will develop to term, though the success rate is still very low (Eppig and O'Brien 1996).

Study of *Acetabularia* has showed that growth and morphogenesis including controllable synthesis of many enzymes and many other proteins are regulated by mechanisms acting in cytoplasm, not by means of alternate transcription of genes. Numerous data, received while researching the enucleated cells, show that specialized protein synthesis matrixes are preserved in cytoplasm long after withdrawing nucleus and that consequently, the synthesis of proteins on these matrixes is controlled by mechanisms acting in the very cytoplasm (Harris 1970). The extremely complicated differentiation can arise under the influence of very simple signals, as it is seen well on the example of *Hydra viridis* explants behaviour (Burnett 1968).

One of the most resistant problems in developmental biology has been that of determining the specific chemical nature of the inducers. In some cases, specific diffusible proteins may be involved; the inducer that acts earliest in frog gastrulas appears to be a growth factor. In other cases, however, insoluble extracellular materials such as collagen and other proteins may be involved in induction. Generally speaking, induction is a phenomenon confined to embryonic tissues (Purves et al. 1997).

Now, it seems to be quite obvious that embryonic development till the relatively late stages happens predominantly on the basis of maternal information, i.e. information containing in egg cytoplasm before the formation of a heterozygous nucleus. Apparently, at these stages the differentiation is reached not by switching on the transcription of certain structural genes, but by turning on the program, being present in egg cytoplasm.

The detection of DGs, if they have ever existed in Nature, is far from implying the existence of an additional way of vertical transfer of genetic information, based not on DNA. In this respect, the hypothesis of pangenesis as an inheritance mechanism is not true. Perhaps, DGs are the same active biological substances like other substrates in oocyte cytoplasm being necessary for embryo's growth. The DG differences are only them to be formed and cumulated as the products of vital activity of specialized cells, tissues and organs of foetus, but not of those of maternal organism, and they can remain this way due to the above stated reasons only in oocyte cytoplasms.

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