Progress in Biophysics and Molecular Biology 98 (2008) 107–117

Contents lists available at ScienceDirect

Progress in Biophysics and Molecular Biology

journal homepage: www.elsevier.com/locate/pbiomolbio

Review

The Turing-Child energy field as a driver of early mammalian development

Yoram Schiffmann

Department of Applied Mathematics and Theoretical Physics, Centre for Mathematica Sciences, Wilberforce Road, Cambridge CB3 0WA, UK

ARTICLE INFO

Article history:
Available online 31 July 2008

Keywords:
Turing-Child field
Mammalian embryo
Assisted reproductive technologies (ART)
Preimplantation genetic diagnosis (PGD)
Mitochondrial activity
Cell division
Differentiation
Cell polarity
Self-organization
Dissipative structure
Living state

ABSTRACT

The equivalence of the early mammalian cells, of importance in assisted reproductive technologies (ART), is considered. It is suggested that this controversial topic can be settled by finding whether the cells are distinguished by the Turing-Child (TC) field, as expressed for example by patterns of mitochondrial activity. The division of the pronuclear embryo is driven by a symmetrical bipolar TC pattern whose experimental shape and chemical nature is predicted by TC theory. This bipolar pattern drives the subsequent cell divisions too, and according to present experimental results all cells are equivalent until compaction since they are not distinguished by the TC field in normal development. Interphase cells exhibit homogeneous mitochondrial activity, or perinuclear, or perinuclear and cortical activity, and these patterns too and the rotational symmetry observed are predicted by TC theory. The first differentiation, into an inner mass cell and the trophectoderm, as well as the formation of cell polarity in the trophectoderm are considered. It is suggested that these two events are driven by a peripheral spherical shell of high energy metabolism in the morula; such a shell is predicted by TC theory in a compacted multicellular sphere whose cells are connected by gap junctions. The experimental patterns of mitochondrial activity in unfertilized oocytes exhibit rotational symmetry or polarity. The shape and the chemical nature of these patterns also are predicted and explained by TC theory in a sphere. The change in the spatial pattern of mitochondrial activity with development is attributed to a change in the spatial pattern of mitochondrial activity and not to physical translocation of mitochondria. The experimental finding that these spatial patterns of mitochondrial activity are observed only in live and not in dead biological material is explained by the TC pattern being biology's unique and universal dissipative structure that requires ongoing specific biochemical reactions and energy dissipation.

Contents

1. Introduction 107
2. Precompaction development 108
   2.1. The instability of the homogeneous state 108
   2.2. Symmetrical division and the equivalence of cells 109
3. Radial polarization and the compacted morula 112
   3.1. The cortical high-energy shell in a multicellular sphere of a TC reaction-diffusion system as the organizer of radial polarization 112
4. Polar oocyte followed by equivalent cells 114
5. Biology's unique and universal dissipative structure 115
   References 116

1. Introduction

The problems of modern medicine concerning regenerative medicine and tissue restoration, *in vitro* fertilization, stem-cell biology and therapeutical cloning, involve 'form regulation' and can be usefully discussed in the framework of Turing-Child theory (Schiffmann, 2001). Consider for example preimplantation genetic diagnosis (PGD) (Braude et al., 2002). It presents a dilemma. The earlier cells are removed for diagnosis the more confident we are that differentiation has not yet occurred. But the removal of one or two cells in an early stage, the two-or-four-cell stage, may involve the removal of a large proportion of the cellular mass of the embryo, with detrimental effects on further developmental potential (Braude et al., 2002). Indeed, for a reconstitution of a whole from a part there should be a correlation between the scale

E-mail address: ys100@cam.ac.uk

0079-6107/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.pbiomolbio.2008.07.001

of organization as expressed by the Turing wavelength and the size of the embryological system (Schiffmann, 2001). In clinical application of PGD, human embryos are successfully biopsied at the 8–2 cell stage even when compact, but beyond the 16 cell stage adhesion is too strong and it is difficult to separate individual cells. It is believed that at the 8–12 cell stage the blastomeres are equivalent and totipotent (Braude et al., 2002), hence the safety of the procedure. Radial polarization is believed to set in when compaction sets in, and this stage is characteristic of the species. For human embryos compaction sets in between 8 and 18 cells (Nikas et al., 1996; Suzuki et al., 1999; Braude et al., 2002).

In the mouse it was believed that the first two or four blastomeres, and perhaps also the first eight, are equivalent and totipotent (i.e. undifferentiated and capable of developing into any type of cell). But in the last few years the equivalence of these first blastomeres has been challenged (Zernicka-Goetz, 2005). The possibility of such an early "prepatterning" has in turn called into question the safety of PGD (Hiiragi et al., 2006a). Leading authorities in developmental biology have adopted these new results and have written that the first two mammalian blastomeres, or the first four, are different and not equivalent (Lawrence and Levine, 2006). This "prepatterning" model enlists "external signals" such as the sperm entry point or the second polar body as a cause of the patterning. A major motivation was the believed involvement of the sperm in patterning in the frog for example (Pedersen, 2001). "The concept of sperm entry point as an important symmetry breaking mechanism is an attractive one, since it is used in a number of other animals such as *C. elegans* and *Xenopus*" (Rossant and Tam, 2004). Not just PGD but also ICSI, intracytoplasmic sperm injection, was said to require a critical reassessment if the new results are valid (Hiiragi et al., 2006a). In Pedersen (2001) it states "there is a sobering implication of the new findings. During human infertility treatments, sperm are injected directly into human eggs. Might this be defining an embryonic axis, or even the future body pattern, of the child? With this possibility in mind, it becomes urgent to find out exactly how sperm affect mouse patterning".

Other scientists could not repeat many of the reported results supporting the "prepatterning" model and the subject has become a hot topic of controversy (Vogel, 2005; Hiiragi et al., 2006a, b; Plusa et al., 2006). However, the usually accepted role of external signals as the source of symmetry breaking, such as the sperm in the frog, gravity in the chick, sperm or light in the *Fucus*, has been challenged. Schiffmann (2006) suggests that symmetry breaking is a true epigenesis based on self-organization via the Turing-Child field. Even in the absence of an external signal, spontaneous symmetry breaking will still occur by virtue of the presence of the Turing-Child system. The choice of which cells will be distinguished in a particular way will occur at random in the absence of any external signal. If a dominant external signal is present, then it biases the choice of the group of cells that will be distinguished. But the Turing-Child system is the fundamental mechanism of symmetry breaking and is required whether the choice of the group of cells that are distinguished occurs at random or is biased by an external signal. Another external signal can override the first signal and then another group of cells can become distinguished. But it makes no fundamental difference which group of cells become distinguished. So correlations between localized external signals, certain groups of early cells, and the later fates of these groups, as found by Zernicka-Goetz (2005) and others, may well exist, but they are not fundamental and should not cause anxiety about the medical procedures mentioned above. Their observation does not cast early cells as "different" in a significant and operational sense. It simply does not matter which group of cells becomes distinguished: they do not start to become different until the Turing-Child (TC) field provides a mechanism. For further discussion see Section 1 in Schiffmann (2006).

Below we show that presently available experimental information points to the TC-equivalence of mammalian cells before compaction and that before then they are not different in any significant sense, which is in accord with the classical belief. Although the first 8 human cells are equivalent, the PGD range of the 8–12 cell stage is when cells begin to diversify. We will also elaborate the suggestion in part 3 of Schiffmann (2007) that cell division, before and after compaction, is driven by self-organization provided by the TC field in an isolated sphere. It involves 'Turing's instability of the homogeneous state' and true epigenesis. We will also elaborate the suggestion in part 1 of Schiffmann (2007) that radial polarization is driven by the spontaneous emergence of an outer spherical shell of high energy metabolism in the compacted morula. Importantly, the radial polarization can explain two things (Maro et al., 1991; Gueth-Hallonet and Maro, 1992; Johnson and McConnell, 2004): (1) cell diversification, the first differentiation, which determines the inner cell mass and the trophectoderm; and (2) cell polarity in the trophectoderm which is the primary epithelium. This is of particular interest since most human cancers are characterized by the deterioration of the ordered cell polarity in epithelial tissues (Wodarz and Nathke, 2007). Since this is in some sense the opposite process of the build-up of cell polarity in development, understanding the latter may be of value in counteracting cancer. A spontaneously emerging TC peripheral pattern in a compacted multicellular sphere, i.e. a cortical/subplasmalemmal high-energy spherical shell, simultaneously drives both cell diversification and cell polarity.

2. Precompaction development

2.1. The instability of the homogeneous state

The early development of the mammalian embryo presents us with a biological realization of Turing's fundamental idea on the 'instability of the homogeneous state' (Turing, 1952): a homogeneous sphere transforms into a non-uniform sphere with an inner ball of high mitochondrial activity and an outer spherical shell with low mitochondrial activity. This 'anti-thermodynamic' transition, the particular form of the non-uniformity, and the chemical nature of the non-uniformity, are explained by TC theory (see Fig. 1).

Consider the hamster. Unfertilized hamster oocytes show homogeneous mitochondrial activity throughout the ooplasm (Fig. 3E in Barnett et al., 1996). Newly fertilized oocytes still show homogeneous mitochondrial activity at 3 h post egg activation (PEA) by sperm (Fig. 1B,C in Barnett et al., 1996). By 6 h PEA, there is an increased mitochondrial activity in the inner ball and decreased mitochondrial activity in the outer shell. By 12 h PEA, when the pronuclei are close to the center, intense mitochondrial activity is observed in the inner ball and the outer shell is devoid of mitochondrial activity (Figs. 1G and 3F in Barnett et al., 1996). A similar pattern is observed at syngamy (fusion of the pronuclei), see Fig. 2B in Barnett et al. (1996).

Barnett et al. (1996) and other groups attribute the spatial changes in mitochondrial activity to physical translocation of the mitochondria, on the basis of the fluorescent probe NAO showing the same spatial patterns as Rh123. However, as discussed in Schiffmann (2007), NAO is sensitive to mitochondrial membrane potential and is not a reliable probe for all mitochondria, active and inactive. Our TC theory, in contrast, attributes the spatial changes in mitochondrial activity to changes in the spatial distribution of mitochondrial activity only, and not to their physical translocation.

Suzuki et al. (2005) used Rh123 and two other mitochondrial fluorescent probes for hamster oocytes. They found a loss of stability of the homogeneous state even earlier. Meiotic metaphase