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Review

Induced pluripotent stem cell technology and aquatic animal species ☆

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ABSTRACT

Aquatic animal species are the overall leaders in the scientific investigation of tough but important global health issues, including environmental toxicants and climate change. Historically, aquatic animal species also stand at the forefront of experimental biology, embryology and stem cell research. Over the past decade, intensive and high-powered investigations principally involving mouse and human cells have brought the generation and study of induced pluripotent stem cells (iPSCs) to a level that facilitates widespread use in a spectrum of species. A review of key features of these investigations is presented here as a primer for the use of iPSC technology to enhance ongoing aquatic animal species studies. iPSC and other cutting edge technologies create the potential to study individuals from "the wild" closer to the level of investigation applied to sophisticated inbred mouse models. A wide variety of surveys and hypothesis-driven investigations can be envisioned using this new capability, including comparisons of organism-specific development and exposure response and the testing of fundamental dogmas established using inbred mice. However, with these new capabilities, also come new criteria for rigorous baseline assessments and testing. Both the methods for inducing pluripotency and the source material can negatively impact iPSC quality and bourgeoning applications. Therefore, more rigorous strategies not required for inbred mouse models will have to be implemented to approach global health issues using individuals from "the wild" for aquatic animal species.

Contents

Abbreviations: EMT, Epithelial–mesenchymal transition; ESC, Embryonic stem cell; F1, First filial generation; HDAC, Histone deacetylase; iPSC, Induced pluripotent stem cell; IRES, Internal ribosome entry site; GSK3β, Glycogen synthase kinase 3 beta; MEF, Mouse embryonic fibroblast; MEK, MAPK/ERK kinase; MET, Mesenchymal–epithelial transition; MSC, Mesenchymal stem cell; PGC, Primordial germ cell; ROCK, Rho Kinase; TGFβ, Transforming growth factor beta.

☆ This paper is based on a presentation given at the 6th Aquatic Annual Models of Human Disease Conference, hosted by the University of Wisconsin–Milwaukee (June 30–July 3, 2013).

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1. Aquatic Animal Models: The Foundation for Stem Cell Research

A host of aquatic animal species amenable to aquaculture, from single cell organisms up through vertebrates, has proven to be highly useful in the study of development, evolution, environment and human disorders. From a historical perspective, aquatic animal models stand at the forefront of experimental biology, embryology and stem cell research. Using freshwater Hydra, Abraham Trembley (1744) showed that halved and quartered individuals could regenerate whole animals, which was striking at the time, but in retrospect not surprising considering that they reproduce mostly by asexual budding and are made up of only two germ cell layers, ectoderm and endoderm (Lenhoff et al., 1986). A century later Ernst Haeckel and others focused attention on the related Siphonophores (e.g. the Portuguese Man o' War), which is a different order of the Hydrozoa, because of their extreme polymorphic characteristics (Haeckel, 1869). In addition to their aesthetics, for which his monograph (1869) drawings won a Utrecht Society for Arts and Sciences gold medal, Haeckel was interested in using their abundant polymorphic traits as a tool to study environmental influences on embryonic patterning and the potential for evolutionary heritability of such traits (Richards, 2008). To this end, he showed that minor changes in water temperature, light intensity and duration, salinity and air saturation (hypoxia/hypercapnia) all had major effects on the patterning of different organ structures. All of these are important aspects of current climate change studies. Taking the approach that structures might be independently influenced and Trembley's lead on regeneration studies, Haeckel took 2-day, cleavage stage embryos and divided them into small groups of cells (blastomeres), finding that some groups of cells could regenerate the whole organism (totipotent), while others could regenerate one to several structures (unipotent, multipotent, pluripotent; Fig. 1). This work created the potential for studying the impacts of environmental exposures on particular features of embryonic development, which is part of cell differentiation studies especially important in today's world. Credit for this work and founding the modern field of "experimental embryology" (which at the time was the "developmental mechanics" movement) was given to two of his students, in experiments performed 20 years later. Hans Driesch (Sea Urchin, 1891 (Driesch, 1891)) dissociated blastomeres to find that individually they

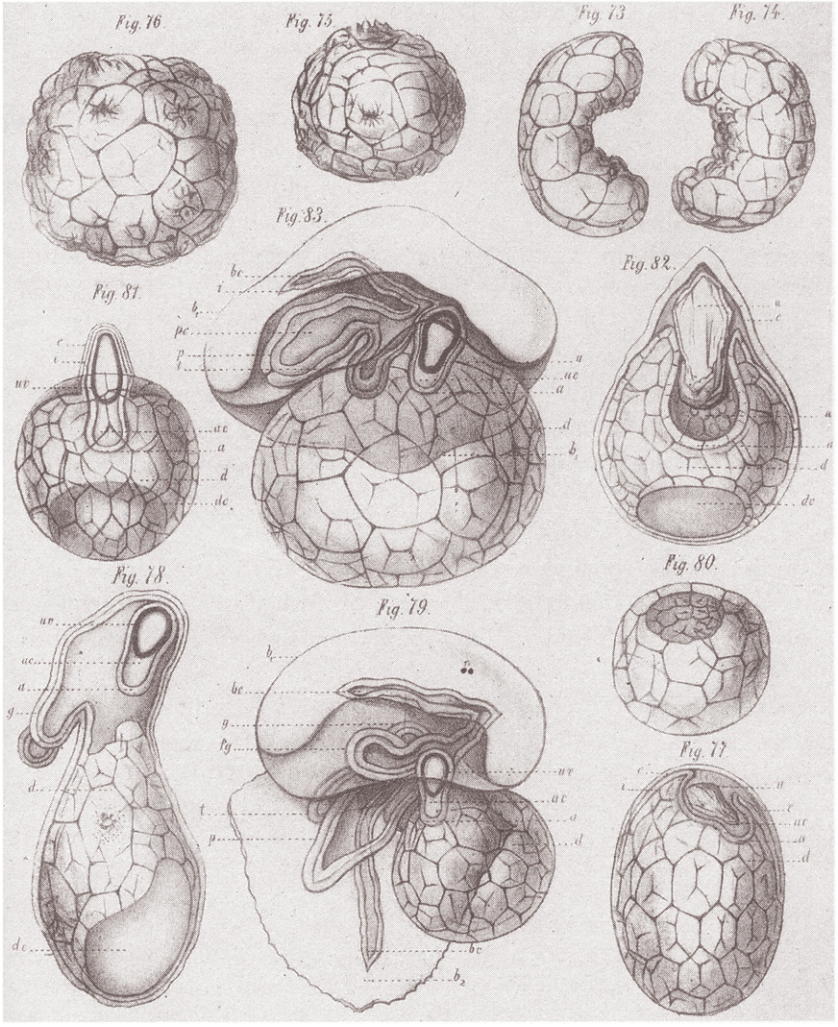

Fig. 1. Illustration of polymorphic structures arising from variable potency dissected siphonophores blastomeres. Siphonophores are Hydrozoans (e.g. the Portuguese Man o' War). Haeckel was interested in using their abundant polymorphic traits as a tool to study embryonic patterning and environmental influences on the heritability of such traits as a mechanism for evolution. Here, Haeckel took 2-day, cleavage stage embryos and divided them into small groups of cells (blastomeres), finding that some groups of cells could regenerate the whole organism (totipotent), while others could regenerate one to several structures (unipotent, multipotent). Freshly bisected cleavage stage embryos (Figs. 73 and 74) and embryos recovering in culture a few hours after bisection are shown (Figs. 75 and 76). Embryos dissected into thirds and cultured for 8 days, produced an embryo with an air sac and two polyps (Fig. 77), a normal 8-day larvae (pluripotent; Fig. 79) and one with multiple structures (multipotent; Fig. 78). Quartered embryos shown (Figs. 80–83) produced one pluripotent larvae (Fig. 83) with all others showing only multipotent stem cell potential. Thus, although all blastomeres appeared the same, they showed varying differentiative potentials, a concept that was complicated by his students Roux & Driesch, but cleared in part by Spemann & Mangold to favor Haeckel's environmental impact model. This figure is a reproduction of drawings from Haeckel's Utrecht Society for Arts and Sciences gold medal award 1869 monograph (Haeckel, 1869).