
IN MEMORIAM



Jacques Signoret (1931- 2007)

Professor Jacques Signoret died last July 2007 at the age of 75. He was a physicist, a naturalist, an eminent embryologist possessing an impressive knowledge and a distinguished teacher. His name has become internationally associated with “Transition Blastuléenne” (Blastulean Transition) which he defined for the first time in 1971 in the urodele Axolotl. Jacques Signoret started his scientific carrier in Paris, first in 1952 as Assistant Professor of Physics in Pr. Louis Leprince-Ringuet’s laboratory, then in 1954 as Assistant Professor of Embryology at the Paris University of Science under the leadership of Pr. Louis Gallien. Research fellowships from NATO allowed him to carry out two post-doctoral positions in the USA, first in 1959 at the California Institute of Technology in Albert Tyler’s laboratory and in 1960 at the Indiana University in Robert Briggs’s laboratory where he succeeded in performing for the first time nuclear transplantations in Axolotl. He came back to France in 1962, bringing back the Axolotl as a laboratory model and was appointed Professor of Embryology at the University of Caen where he taught until 1998. He extended his teaching activity by writing Developmental Biology textbooks in collaboration with Professor Alain Collenot (Signoret and Collenot, 1991, Collenot and Signoret, 2000). He also actively participated in the creation of the French Society of Developmental Biology (SFBD) and organized its first meeting in 1977 in Caen. He contributed to the creation of the European Developmental Biology Organisation (EDBO) and became its Vice-President (1976-1981) then its President (1982-1988). These responsibilities led him to participate as representative of EDBO in the European Council (1982-1988) and the European Union (EU) (1989). Jacques Signoret was a very dexterous experimenter working during his whole career on Urodeles. His main scientific contributions can be divided into four themes: 1) the teratogenic action of LiCl on cephalogenesis in the Salamander *Pleurodeles waltl*; 2) the application of the nuclear transplantation method to Axolotl and *Pleurodeles waltl*; 3) the cytogenetic aspects of the cell cycle and the concept of “Blastulean Transition” and 4) the degradation of transcripts during early development.

The teratogenic action of LiCl on cephalogenesis in the Salamander *Pleurodeles waltl*

Normal and teratologic cephalogenesis in the Salamander *Pleurodeles waltl* was the subject of the PhD of Jacques Signoret. For this study, he incubated early gastrula stage embryos in a LiCl solution (Signoret and Gallien, 1957). The main abnormalities resulting from this treatment are localized in the more rostral and dorsal structures of the embryos such as synophthalmia and even anophthalmia. To study the anatomy of these larvae by dissection later than the feeding stage, he associated an abnormal embryo and a normal one at the level of the tail bud. Such a parabiosis that he termed telobiosis allowed the development until metamorphosis of the anterior parts without any mechanical disturbance (Signoret, 1960).

The application of the nuclear transplantation method to Axolotl and *Pleurodeles*

As a post-doctoral fellow in the laboratory of Pr. Robert Briggs, Jacques Signoret applied the nuclear transplantation techniques previously created in the Anura by Briggs and King in 1952 (Signoret *et al.*, 1961) to Axolotl. After coming back to France to the laboratory of Pr. Louis Gallien, he applied the technique to the Salamander *Pleurodeles waltl*, perfecting the activation of the oocytes by an electric shock in order to easily obtain large quantities of activated oocytes (Signoret and Fagnier, 1962). The experiments carried out with Axolotl demonstrated that nuclei taken from different germ layers at progressively ageing stages lost their capacity to induce the normal development of the newly reconstituted egg (Signoret *et al.*, 1964). These results led Jacques Signoret to investigate the origins of these impairments, more precisely at the level of the chromosomes during the different phases of the cell cycle (Signoret, 1968).

The cytogenetic aspects of the cell cycle and the concept of the Blastulean Transition

In 1965, Jacques Signoret proposed a pioneer technique by which clear pictures of the chromosomes in Axolotl blastulae can be obtained (Signoret, 1965). He then described the transitory appearance of a pseudo-satellite on the distal fragment of chromosome 7, followed by its progressive disappearance at the mid-blastula stage, and suggested that this reproducible phenomenon corresponded to selective “chromatin diminution” (Signoret and Lefresne, 1969). This last result drove him to study the modalities of DNA replication, establishing that an asynchronism also occurs at the mid-blastula stage (Signoret and Lefresne, 1970).

IN MEMORIAM

From 1971 with Dr. Jacques Lefresne, his collaborator during 30 years, Jacques Signoret particularly focused on the analysis of cellular dynamics during early development. He judiciously chose the Axolotl egg as a model because the duration of its early development is about four times longer than that of *X. laevis*. A meticulous chronological description of Axolotl cleavages was undertaken and cellularization indices which led to an objective marking of each stage were defined. After a first phase of synchronous and rhythmic cellular multiplication, a progressive desynchronization, characterized by a variable lengthening of the duration of the cellular cycles, then occurs on and after the tenth segmentation cycle. Jacques Signoret named this developmental event: "La Transition Blastuléenne" (Blastulean Transition; Signoret and Lefresne, 1971, Signoret and Lefresne, 1973). Since then, this concept is internationally known and has been studied in other models (the MBT or Mid Blastula Transition), although it does not always have the same meaning nor the same determinism as in Axolotl.

In this urodele, during the synchronous cleavage period, analysis of the cell cycle showed that for each blastomere, the beginning of DNA replication occurred as early as the end of mitosis (telophase) before the reconstitution of the interphase nucleus, implying the absence of a G1 phase (Signoret and Lefresne, 1974). This analysis also established evidence for the presence of a G2 phase during which an incorporation of radiolabeled RNA precursor was detected, suggesting that transcriptional activity is necessary for entry into M phase (Signoret and Lefresne, 1975).

During the Blastulean Transition, autoradiographic analysis of the incorporation of DNA precursor, performed on individual known-aged blastomeres, revealed the progressive introduction of the G1 phase whose duration is variable from one cell to another (Lefresne *et al.*, 1998). This variability could account for the lengthening and desynchronization of cell cycles. At the 12th cycle, all blastomeres have a cycle length which is longer than during the synchronous cleavage period, strongly suggesting that at this stage all cells possess a G1 phase. Under these conditions, the Axolotl Blastulean Transition is limited *stricto sensu* to the 10th-11th and 12th embryonic cell cycles. The G1 phase appearance would correspond to the exhaustion of a factor necessary to enter into S phase and would require the expression of the zygotic genome. The synthesis of this factor would follow particular kinetics with a decreasing exponential distribution as defined by the statistical model proposed by Signoret (Signoret, 1977). During the desynchronization phase, the notion of segmentation cycle duration disappears in favour of the statistical distribution of individual cycles times. All these results support a DNA-replication checkpoint for cell cycle control and constitute the "nuclear" basis of the Blastulean Transition.

The degradation of transcripts during early development

From 1994, in collaboration with Pr. Yannick Andéol, Jacques Signoret addressed, at the molecular level, the question of temporal regulation of early embryonic events associated with the Blastulean Transition. As this transition can be considered as the switch from maternal to zygotic programs (Signoret, 1980), it could result from several processes involving maternal mRNA decay and early activation of zygotic genes controlling this degradation. To study the RNA stability during early development, an *in vivo* heterologous *Xenopus*/Axolotl system was developed. Exogenous *c-myc* *Xenopus* RNAs were injected into the Axolotl oocyte or fertilized egg and the existence of several sequential developmental timers controlling degradation of these injected molecules was shown (Andéol *et al.*, 1995). These studies led to the suggestion of a *de novo* synthesis of *c-myc* RNA molecules and a possible post-transcriptional RNA amplification (Andéol *et al.*, 1998). This process was interpreted as being linked to the existence of an RNA-dependent RNA polymerase (RdRp) activity present in the egg and whose characteristics are currently being investigated in Axolotl (Montreau *et al.*, 2004). The successive themes of the research of Jacques Signoret illustrate pertinently the evolution of academic experimental embryology into contemporary developmental biology, associating in its experimental procedures the techniques and concepts of genetics and molecular biology.

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