Chapter 11
Aquatic Invertebrate Dormancy and Medicine

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Abstract Aquatic organism dormancy has interesting medical applications, which include dormancy in parasite species, dormancy in intermediate hosts of parasites, and several diseases that seem to present a kind of dormancy. Among these, the most remarkable is the state of dormancy in some types of cancer, one of the most serious human diseases. Holmes, in the middle of the twentieth century, recognized, as one stage of cancer, a long period of delay in carcinogenesis, similar to dormancy. Later on, Makrushin described an "evolutionary hypothesis" of carcinogenesis and recognized this disease as an old genetically related program—a kind of archaic program that is normally dependent on "sleeping" genes. His hypothesis did not explain several important peculiarities of cancerous tumors. The most important one is fast dissemination of the tumor and creation of a large number of metastases. In this chapter, we suggest another hypothesis of carcinogenesis, also related to sleeping genes, that is responsible for the metabolic rate found in dormant cells and postdiapause cells. A possible hormonal mechanism underlying this hypothesis is discussed.

Keywords Carcinogenesis · Evolutionary origin · Medical aspects of dormancy · Metabolic theory

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11.1 Introduction

Dormancy is a profound and ancient adaptation found in a wide spectrum of plants and animals in all habitats (Alekseev 1990). One of the most fascinating and profound adaptations related to dormancy is diapause (Danilevsky 1961). In diapause the switch between active and dormant states is driven by a complicated and multilevel hormonal mechanism, which usually includes a photoperiodic pacemaker and several other signals coming from the environment. Temperature, food limitation, and some other stress factors of different origins are known as external drivers of dormancy induction (Alekseev et al. 2007; Nelson et al. 2010). In recent years, dormancy studies on a wide variety of topics have demonstrated that it may be possible to develop diapause switch mechanisms to create novel applications in biotechnology, science, and medicine (Alekseev et al. 2006, 2007; Alekseev 2010).

Several aspects of aquatic organism dormancy can also be interesting in medicine. For example, dormancy in mosquito larvae can be important for distribution of several tropical diseases in a polar direction from the equator (Vinogradova 2007). Many cyclopoid copepods are intermediate hosts for parasitic organisms such as protists and worms. The peculiarities of dormancy in such cases become crucial factors for parasitic diseases in humans and in human-cultivated organisms (Evseeva 1996). It might be useful to consider dormancy and its genetic mechanisms as a model of some medical situations related to activation/suppression processes that are also observed in some human diseases (Table 11.1). Diapause hormonal and biochemical mechanisms may also parallel mechanisms of lethargic dream syndrome, some posttraumatic syndromes, some categories of disability, carcinogenesis, and aging (Craigie et al. 1951; Makrushin and Lyanguzova 2006).

The most fascinating hypothesis, however, could involve the possible impact of this dormancy theory on our understanding of carcinogenesis in humans.

11.2 Makrushin's Evolutionary Hypothesis of Carcinogenesis

Makrushin (2004) was the first person to propose that destructive and proliferative phenomena in dormancy in some lower invertebrates are similar to known destructive processes in cancer in vertebrates. He speculated that there is a parallel between these particular pathological processes in vertebrates and seasonal body reduction associated with formation of the resting stage known to occur in primitive metazoans (*Spongia*, Hydrazoa, etc.) According to his hypothesis, cancer cells appear as a result of regressive development of tissue cells caused by stochastic activation of an ancient program (a sleeping gene) for dormancy induction.

Table 1.1 Physiological states of organisms based on metabolic level and on the cause of the arrestation of vital functions (after Alekseev et al. 2007 with changes)

Active Life	**Boundary States**	**Dormancy or Hypobiosis**					
Normal metabolism, development, growth, and breeding	Short-time metabolism declining	Suppressed metabolism, with long-time cessation of development, growth, and breeding					
		Quiescence			**Diapause**		
		(hibernation and/or aestivation) driven by unfavorable/favorable conditions for life			driven by hormones, induced by both signal and vital factors		
	Sleep, physiological stress, thermal shock, some illness and medical/artificial coma in humans	**Latent life**			**Suppressed life**		
		Cryptobiosis	Anabiosis	Abiosis	**Superpause**	**Mesopause**	**Oligopause**
					More than 1 year	3–12 months	Less than 3 months

When the idea of dormancy in cancer cells was first published, the hypothesis was not taken seriously (Craigie et al. 1951). There was very little critique among medical scientists and biologists, and the hypothesis was by no means considered testable. But, to everyone's surprise, data obtained from molecular genetic studies of dormancy in the nematode *Caenorhabditis elegans* supported this idea of a common genetic basis for diapause and aging (Gerisch and Antebi 2004).

Recent studies have suggested that in *C. elegans*, gene expression changes choose between the third larval diapause and reproductive development. A cascade of genes and their gene products mediates this choice between diapause and active development in *C. elegans*. These include *daf-9* (a cytochrome P450 gene related to steroidogenic hydroxylases) and *daf-12* (a nuclear receptor gene encoding for lipophilic hormones that control the physiological status of the organism) (Gerisch and Antebi 2004).

A simple model is that the *daf*-9 gene produces a hormone regulating *daf-12*. Its gene product bypasses diapause, promotes reproductive development, and perhaps also shortens the life-span. This hormone might be a sterol (Gerisch et al. 2001). Expressed in potential endocrine matter, *daf-9* appears to control developmental decisions for the entire organism. Recent findings implicate *daf*-9 as a central point of developmental control, producing hormonal signals that regulate the life history of *C. elegans* (Gerisch and Antebi 2004).

The choice between development and dormancy can be regulated by several substances. Insulin is such a substance. Other signals that control the diapause program throughout the body are special peptides (e.g., transforming growth factor β (TGFβ) and serotonergic signaling) (Finch and Ruvkun 2001). Insulin and TGFβ peptides are synthesized in response to environmental stimuli, mainly from sensory neurons. Alternatively, a complex of the *daf-3* and *daf-5* genes may effect a shift to diapause in adverse environments. TGFβ inactivates *daf-3* and *daf-5*, thus allowing reductive development (Gerisch et al. 2001). There is evidence that both insulin and TGFβ receptors convey signals through downstream secondary endocrines and that *daf-2* regulates diapause and the life-span through systemic signals (Apfeld and Kenyon 1998; Wolkow et al. 2000). The mechanism of verification, based on experiments with mutants, is in other publications (Alekseev 2010; Alekseev et al. 2006).

The genes *daf-9* and *daf-12* linked with diapause have now been found in a very wide range of organisms, from yeasts to vertebrates. The genetic program coding for dormancy can either be actively used by the organism or simply kept "in reserve" by the genome without being expressed. This discovery by molecular biologists comes back to Makrushin's hypothesis of the evolutionary origin of cancer in vertebrates that appears as activation of sleeping dormancy genes. Makrushin also postulated that the final aim of a dormant tumor, which is almost never realized, is creation of a kind of dormant embryo similar to one produced by primitive Coelenterata organisms in harsh environmental conditions. This statement is not well supported by medical observations.

11.3 Hypothesis of Metabolic Mechanism Breaking in Cancer Cells

A new version of the hypothesis of carcinogenesis based on dormancy gene expression has been suggested to overcome some contradictions in Makrushin's theory (Alekseev et al. 2006). At the cancer stage of a dormant tumor, there is a sudden shift from a quiet state to a state of fast division and dissemination of new fast-growing "seeds" called metastases. Cells in metastases have a higher metabolic rate than normal cells, so the metastases grow very fast and finally kill the organism within a short time.

We propose that a similar mechanism responsible for diapause, for normal metabolism, and also for more active metabolism can be observed in diapausing organisms after termination of dormancy. Further, this mechanism results from activation of a single gene (or a group of genes?) and is hormone driven. Normal metabolism is the standard state of cells in an organism, and it is regulated by a balance between the hormone activator and inhibitors of metabolism. Both balance and misbalance, as normal adaptations to environmental demands, have, in fact, been demonstrated in the molting and life cycles of some decapods (Aiken 1969; Alekseev 1998).

In this way, carcinogenesis can thus appear as the result of an abnormal hormonal misbalance in some cells. The mechanism behind this could be triggered in a cell as a result of gene damage, whether from chemicals, radioactive or viral agents, or other causes. In this hypothetical cell, some normally sleeping genes responsible for metabolism would suddenly become activated, and the organism would lose control of metabolism and division in these cells. In a normal, healthy organism, the immune system is able to recognize and kill these out-of-control cells. In our supposed scenario, however, such a cell would not be killed by the immune system and would start intensively reproducing itself like a postdiapause embryo, developing into a carcinogenic tumor. Among the possible explanations for a scenario so negative for the organism could be many reasons for immune system weakness: stress, other illness, age, etc. This explains the so-called poly-reason nature of carcinogenesis.

In our hypothesis, in contrast to Craigie's and Makrushin's hypotheses, cells in cancer tumors are similar to postdiapausing embryonic cells driven by an out-of-control hormone activator. They are characterized by higher metabolic activity and division, as shown by a reactivated *Daphnia* embryo (Arbacauskas and Lampert 2003).

Our hypothesis, if substantiated through testing, will provide clinical scientists with dormancy-derived hormones (many of them are known!) as a new instrument for cancer research and treatment. With this comes the promise of new medicines or types of treatment aimed at normalizing the balance in hormonal mechanisms of cell metabolism.

11.4 Conclusion

Diapause is a very profound and ancient adaptation found in many classes of aquatic animals and plants. It appears likely that there is a monophyletic origin for this adaptation, as there are similarities in the molecular basis and genetics of diapause mechanisms among organisms. Research on diapause in aquatic organisms opens up many new scientific directions and technologically important applications. When medical conditions originate from a misbalance in the activation/suppression process, diapause may offer a useful model for innovative treatment approaches. A new hypothesis of the carcinogenesis process states that tumor cells parallel postdiapause embryonic cells.

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