Chapter 3
Stem Cells in Immortal *Hydra*

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Abstract *Hydra*'s potential immortality and extensive capacity to regenerate and self-renew is due to the presence of three distinct stem cell lineages: ectodermal and endodermal epithelial stem cells, and interstitial stem cells. Over the last few years, stem cells in *Hydra* became well-defined in cellular terms of their biology. More recently, efforts using the nearly unlimited potential for tissue manipulation combined with functional transgenesis have shed light on the molecular control mechanisms involved. Here I review those efforts in an attempt to give both a historical perspective and an update on the recent experimental highlights. In particular, I will focus on six aspects of stem cells in Hydra: (i) their continuous transition through the proliferation/differentiation switch; (ii) their rapid responses to signals from the cellular environment; (iii) the emerging importance of Wnt and Notch signaling in controlling stem cell behavior; (iv) the role of chromatin modification in terminal differentiation; (v) the observation of transdifferentiation in some of the stem cell progeny; and (vi) the implications for the evolution of germ cells, ageing and cancer. Together, these findings seem to indicate that *Hydra* not only provides insights into signalling pathways involved in stem cell differentiation in the Bilaterian ancestor; they also demonstrate that despite morphological and functional differences, and more than 500 million years of phylogenic separation between *Hydra* and human, common signaling pathways are responsible for stem cell maintenance, lineage determination, and differentiation.

Keywords Epithelial stem cell, evolution of development, Hydra, interstitial stem cell, Notch, senescence, Wnt, Weismann's doctrine

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3.1 Hydra, a Classical Model System in Developmental Biology

Cnidaria are sister group to the bilaterians (Collins, 1998; Philippe et al., 2005) and therefore provide information for reconstructing the early history of bilaterian developmental mechanisms. They consist of two epithelia, the ectoderm and the endoderm surrounding a gastric cavity; and they are the first in evolution that have a defined body plan, a nervous system, and a tissue layer construction. Cnidarians such as the freshwater polyp *Hydra* have a long history as model systems in developmental biology because of their remarkable capacity to regenerate. This ability for self-organization is at least partially due to the continuous presence of stem cells with high self-renewal capacity and high phenotypic plasticity in adult tissue. The capacity for constant renewal is also the main reason behind Hydra's potential immortality.

In molecular terms, *Hydra* as all other members of the phylum Cnidaria is astonishingly complex. The genomes in different *Hydra* species vary in size but in general are large with *H. vulgaris* having a genome of 1,250 Mbp (Zacharias et al., 2004). Moreover, Cnidaria not only have about the same number of genes as human and share most of their genes with human (Miller et al., 2005; Miller et al., 2007) but their protein sequences, surprisingly, are often more similar to mammalian sequences than to those from fly and worm (Kortschak et al., 2003). Thus, at the level of genomic complexity and gene complement, *Hydra* is much more complex than previously imagined. Novel computational tools and the development of genomic resources over the past few years have brought a new perspective on *Hydra* as a model organism. A National Science Foundation-funded large-scale *Hydra* EST Project (www. hydrabase.org) resulted in 170,000 ESTs. A National Human Genome Research Institute-funded *Hydra* genome project at the J. Craig Venter Institute currently provides 6x coverage of the *Hydra magnipapillata* genome with an assembled draft genome sequence appearing later in 2007. For database searches, Georg Hemmrich in my group has established a local Blast-platform, www.compagen.org, containing selected raw genomic (NCBI Trace archive) and EST (NCBI dbEST, JGI) sequence datasets from sponges and cnidarians up to the lower vertebrates (Hemmrich and Bosch, in prep.).

While there is no evidence that *Hydra* is simpler in molecular terms than vertebrates nor that *Hydra* cells are fundamentally different from those in mouse or human, there may be a profound difference in the differentiation potential and plasticity of the cells between *Hydra* and vertebrates. Vertebrates depend on specialized cells with limited differentiation potential to perform sophisticated functions. Cells in *Hydra*, in contrast, are capable to produce and receive positional signals continuously even in adult tissue and, therefore, have features which most cells in vertebrates have only during the short period of embryogenesis. It is this feature which makes adult *Hydra* tissue different from tissue of all other invertebrates and vertebrates.