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METABOLISM AND STEM CELLS (D NAKADA, SECTION EDITOR)

Steroid Hormones and the Physiological Regulation of Tissue-Resident Stem Cells: Lessons from the *Drosophila* Ovary

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Abstract
Purpose of Review Stem cells respond to local paracrine signals; more recently, however, systemic hormones have also emerged as key regulators of stem cells. This review explores the role of steroid hormones in stem cells, using the *Drosophila* germline stem cell as a centerpiece for discussion.
Recent Findings Stem cells sense and respond directly and indirectly to steroid hormones, which regulate diverse sets of target genes via interactions with nuclear hormone receptors. Hormone-regulated networks likely integrate the actions of multiple systemic signals to adjust the activity of stem cell lineages in response to changes in physiological status.
Summary Hormones are inextricably linked to animal physiology and can control stem cells and their local niches. Elucidating the molecular mechanisms of hormone signaling in stem cells is essential for our understanding of the fundamental underpinnings of stem cell biology and for informing new therapeutic interventions against cancers or for regenerative medicine.

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Introduction

Physiological homeostasis requires hormones, which are circulating chemical messengers that ensure that cells with diverse functions in tissues throughout the body work in a coordinated manner to maintain organismal health [1, 2]. Hormones are produced by specialized cells in highly innervated glandular tissues, such as the pituitary and thyroid, and function as long-distance signals to communicate changes in physiological conditions, including altered carbohydrate and lipid metabolism, growth, sexual maturation, and stress. Hormones affect every organ system in the body; it is therefore not surprising that tissue-resident stem cells, which are the sources of new cells within established tissues, can sense and respond to circulating hormones as do terminally differentiated cells [3–7]. In particular, steroid hormones, known as vital modulators of organismal growth, developmental transitions, and secondary sex characteristics, have recently achieved greater prominence as new roles for them in the regulation of stem cell function have emerged (Table 1) [3, 4]. Elucidating the fundamental molecular mechanisms of how hormonal signals are sensed and interpreted by stem cells, in their native environment, is critical for the development of future therapeutic strategies for regenerative medicine and cancer treatment.

In this review, we highlight new discoveries about the role of steroid hormones in the control of tissue-resident stem cells. We focus on the *Drosophila* female germline stem cell (GSC), a model system that illustrates how stem cells respond to steroid hormones in a physiological context. We summarize the

Table 1 Summary of the known roles of nuclear hormone receptor signaling in tissue-resident stem cells

Receptor	Ligand	Stem cell	Role	References
Drosophila				
EcR	Ecdysone	Ovarian germline stem cell	Directly and indirectly promotes proliferation and maintenance; indirectly promotes differentiation of daughters	[8–12]
EcR	Ecdysone	Testes cyst stem cell	Promotes proliferation and maintenance; indirectly promotes maintenance of germline stem cells	[13]
EcR	Ecdysone	Larval neuroblast	Promotes cell cycle exit and terminal differentiation	[14]
Mouse				
PR	Progesterone	Mammary stem cell	Directly promotes proliferation and maintenance	[15, 16]
ER	Estrogen	Mammary stem cell	Indirectly promotes proliferation and maintenance	[15, 16]
ERα	Estrogen	Hematopoietic stem cell	Directly promotes proliferation and maintenance	[17]
ER	Estrogen	Muscle precursor cell (satellite cell)	Indirectly promotes quiescence	[18]
TR	Thyroid hormone	Hair follicle stem cell	Indirectly promotes proliferation, migration out of the niche	[19•]
PPARδ	Fatty acids	Intestinal stem cell	Directly promotes proliferation and maintenance in response to dietary fatty acids	[20]
Nurr1	None	Hematopoietic stem cell	Directly represses proliferation / promotes quiescence	[21]
TLX	Unknown	Neural stem cell	Directly promotes proliferation and maintenance	[22]
VDR	Vitamin D	Neural stem cell	Directly promotes proliferation and survival; promotes differentiation of daughter cells to terminal fates	[23•]
RAR	Retinoic acid	Hematopoietic stem cell	Indirectly promotes differentiation	[24•, 25]

major themes of how diverse steroid hormones regulate stem cell fate and the differentiation of stem cell progeny, using examples from *Drosophila* and mammalian stem cell lineages to suggest key areas for future study. Finally, we discuss the implications of steroid hormone control of stem cell fate and function for human diseases and potential regenerative medicine applications.

Tissue-Resident Stem Cells: an Essential Source of Cells for Tissue Homeostasis and Regeneration

Most adult tissues require the activity of stem cells for homeostasis and proper function. Tissue-resident stem cells have two defining characteristics: they self-renew, maintaining a stem cell pool throughout the life of the organism, and they generate daughter cells that can differentiate into one or more distinct terminal fates [26]. These properties ensure that tissue integrity and cellular diversity are maintained in the face of normal cellular turnover, tissue remodeling, or damage. Adult stem cells are lineage-restricted, such that they only generate daughter cells specific to their tissue of residence. For example, mammalian hematopoietic stem cells replenish all of the mature cells in the blood cell lineage [27], while intestinal stem cells give rise to the absorptive and secretory cell types that compose the intestine [28]. Stem cells have also been identified in tissues with less frequent cellular turnover, such as the brain [29], or, conversely, that undergo dramatic remodeling during adult life, such as the mammary epithelium [4]. Given their central roles in tissue homeostasis, stem cells must be tightly regulated to prevent tissue overgrowth or atrophy.

A major challenge in the field of stem cell biology is to understand at the molecular level the mechanisms by which stem cells maintain their defining properties and adjust their activity in the context of intact organisms. Over the years, a variety of model stem cell systems ranging from invertebrates to mammals have emerged, largely due to advances in lineage tracing that enable stem cell identification. Of these, the fruit fly, *Drosophila melanogaster*, stands out as a pioneer for many key experimental demonstrations underlying current models for the maintenance of stem cell identity and function

[30]. Like mammals, *Drosophila* have multiple tissue-resident stem cell populations that sustain the production of differentiated cells. The ease with which *Drosophila* is reared; the wealth of available genetic tools for cell-specific gene manipulation; the amenable cell biology of their stem cell-supported tissues; and the remarkable evolutionary conservation of molecular, cellular, and physiological mechanisms make them a powerful model organism for stem cell research.

The *Drosophila* Female Germline Stem Cell: a Model System for Studying Stem Cell Regulation by Steroid Hormone Signaling

The *Drosophila* female GSC system has been a major experimental model for the elucidation of the cellular and molecular basis of stem cell niches and for exploring how whole-body physiology can impact stem cell lineages. Female GSCs give rise to the cellular precursors for *Drosophila* oocytes [31, 32]. GSCs are housed in a structure called the germarium (Fig. 1a, b) at the anterior tip of each of the 14 to 16 ovarioles that comprise the *Drosophila* ovary (Fig. 1c). GSCs reside in a somatic niche composed of terminal filament cells, cap cells, and a subset of escort cells (Fig. 1a). The niche produces bone morphogenetic protein (BMP) signals that are necessary for GSC self-renewal [32]. GSCs are physically attached to cap cells via E-cadherin and divide asymmetrically to create a posteriorly displaced cystoblast, the daughter cell destined for differentiation, while retaining the other daughter as a GSC in the niche. The cystoblast divides four more times with incomplete cytokinesis. One of the cells of the resulting 16-cell cyst becomes the oocyte, while the other 15 become nurse cells that support oocyte development and produce factors required by the early embryo [31]. Somatic follicle cells derived from follicle stem cells (FSCs) surround each germline cyst to form an egg chamber or follicle that subsequently leaves the germarium (Fig. 1a). The anatomy of the *Drosophila* ovary, coupled to the availability of sophisticated genetic and cell biological tools, greatly facilitates the analysis of GSCs and their descendants. Specifically, GSCs and their progeny exist in a predominantly linear arrangement,

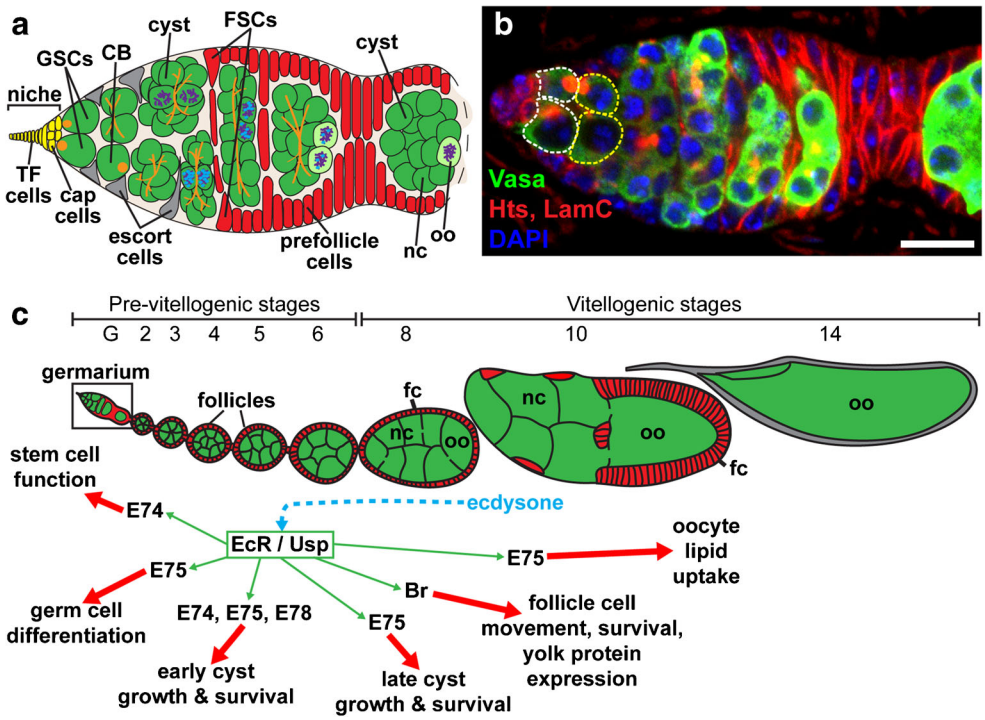

Fig. 1 The steroid hormone ecdysone controls multiple steps of *Drosophila* oogenesis. Female germline stem cells (GSCs) reside in a germarium (**a**, **b**) at the anterior tip of each of the 14–16 ovarioles (**c**) that compose the *Drosophila* ovary. **a** GSCs are anchored to adjacent cap cells that, along with terminal filament (TF) cells, send signals to maintain GSCs in a self-renewing fate. GSCs divide to form daughter cells (cystoblasts, CB), which divide four additional times to form 16-cell germline cysts composed of nurse cells (nc) and an oocyte (oo). Escort cells (*gray*) signal to germ cells to promote differentiation. Follicle stem cells (FSCs) divide to form prefollicle cells, which surround the 16-cell germline cyst, giving rise to a follicle that leaves the germarium. Prefollicle cells give rise to a variety of specialized follicle cells (fc; *red*) that form an epithelial monolayer around each cyst. **b** Confocal micrograph of a germarium immunolabeled with anti-Vasa (*green*; labels all germ cells), anti-Hts (*red*; labels early germline-specific organelles called fusomes and follicle cell membranes), anti-Lamin C (*red*; labels the nuclear envelope of cap cells), and DAPI (*blue*; labels all nuclei). *Dashed lines* outline GSCs (*white*) and cystoblasts (*yellow*). Scale bar, 10 μm. **c** Summary of ecdysone-regulated processes in the ovary. Ecdysone is produced by older follicles and stimulates the EcR/Usp complex expressed throughout the ovary. Activation of the complex results in a variety of cellular responses mediated by distinct ecdysone-responsive transcription factors, such as E74, E75, E78, and Br

providing in a single ovariole an orderly time course of their recent developmental history (Fig. 1c). *Drosophila* female GSCs therefore remain one of the best models for the study of stem cell function and regulation at the single cell level in vivo. In particular, definitive evidence that stem cells are controlled by multiple endocrine factors, including steroid hormones, tied to the physiological status of the organism was obtained in the *Drosophila* GSC system [32].

Steroid Hormone Signaling Is Essential for GSC Function and Development of Their Progeny

The best characterized steroid hormone in *Drosophila* is ecdysone, which is structurally similar and functionally analogous to the mammalian sex steroids estrogen and progesterone [33, 34••]. Ecdysone signals by binding to the ecdysone receptor, a heterodimeric complex of two conserved nuclear hormone receptors encoded by *ecdysone receptor* (*EcR)* and *ultraspiracle* (*usp*) [35]. Binding of ecdysone to its receptor transcriptionally activates a wide variety of target genes, including transcription factors that direct cell-specific target gene regulation [36]. *Drosophila* synthesize ecdysone from dietary plant-based cholesterols through a multi-step enzymatic process [37]. During development, ecdysone is synthesized in an endocrine organ called the ring gland and regulates many processes, including organismal growth, ovarian cell differentiation, and ovary size [10, 36, 38, 39, 40••], whereas in adults, it is produced predominantly in late-stage follicles in the ovary [37, 41, 42].

In adult females, ecdysone is an essential regulator of female metabolism and reproduction [34••, 42, 43••, 44••]. For example, during copulation, males transfer sex peptide, a seminal fluid peptide that stimulates a variety of neurons to induce post-mating changes in females, including up-regulation of ecdysone synthesis in the ovary [43••, 45–47]. Ecdysone acts in the female central nervous system to promote a metabolic state supportive of oogenesis [34••]. Specifically, knockdown of ecdysone signaling in neurons reduces feeding rates in female flies, as well as decreases whole-body triglyceride and glycogen storage, leading to decreased egg production [34••].

Ecdysone signaling also has multiple roles during oogenesis to ensure efficient egg production under favorable conditions (Fig. 1c) [42, 44••, 48–50]. *EcR*, *usp*, and the ecdysone target genes *broad* (*br*), *ecdysone-induced protein 74EF* (*E74*), *ecdysone-induced protein 75B* (*E75*), and *ecdysone-induced protein 78C* (*E78*) are all required for oogenesis [48, 49, 51••, 52–54]. Ecdysone signaling mediates the increase in GSC proliferation induced by the first mating of young females [43••] and is necessary for sustained GSC proliferation and self-renewal [8]. Ecdysone signaling is also necessary for the differentiation of germ cells and the individualization of germline cysts into discrete follicles [9••, 10, 11, 12••]. As oogenesis proceeds, ecdysone signaling is required for the growth and survival of germline cysts at two important developmental stages. Germline cysts harboring mutations in *EcR*, *E74*, *E75*, or *E78* frequently degenerate at stage 4/5 [48, 49, 51••], and *E75* is thought to control a nutritional checkpoint at stage 8/9 that permits reabsorption of follicles in starved females [55]. Ecdysone signaling promotes vitellogenesis by upregulating yolk protein expression in follicle cells [56] and stimulating lipid accumulation in oocytes [34••]. For the latter, activation of EcR and E75 results in the transcriptional activation of genes involved in lipid metabolism, including the transcription factor *SREBP* [34••]. Taken together, these data demonstrate that ecdysone signaling controls a wide variety of cellular functions in the ovary.

Ecdysone regulation of the GSC lineage involves direct and indirect mechanisms. Proliferation and self-renewal are impaired in *usp* and *E74* mutant GSCs, indicating that ecdysone signals are directly received by GSCs to control proliferation and maintenance [8]. Ecdysone also stimulates GSCs indirectly through neighboring somatic cells. Knockdown of *EcR*, *usp*, *E75*, or the EcR co-activator *tai* in escort cells and early follicle cells results in decreased GSC number and proliferation [10, 11, 43••]; however, it is unclear whether a requirement for ecdysone signaling during GSC establishment may contribute to these effects. Of note, the regulation of GSC function by ecdysone is largely independent of systemic insulin signaling, despite the fact that neural insulin signals are also necessary for GSC proliferation and, indirectly, for their maintenance [8, 43••, 57].

Recent evidence suggests that ecdysone signaling is also required in the follicle cell lineage. A genetic screen designed to find ecdysone-responsive genes required for oogenesis identified several genes that modulate the fate and proliferative capacity of FSCs [12••]. FSCs give rise to the follicle cell lineage, which is required for proper germline development and ultimately forms the eggshell [31]. Ecdysone signaling is well known to regulate follicle cell function at later stages of oogenesis [52–54, 58, 59••, 60, 61••, 62], but its roles in early somatic cell differentiation remain largely undescribed. While our data suggest that ecdysone signaling controls FSC function [12••], it remains to be investigated whether this occurs through similar molecular mechanisms as those controlling GSCs. The screen identified a mixture of downstream targets, some common to GSCs and FSCs and some with separate effects, suggesting that ecdysone signaling may control the two stem cell populations largely independently. Moreover, ecdysone signaling in escort cells and in the FSC lineage indirectly regulates the differentiation of GSC descendants. Reduction of *EcR* or *E75* in escort cells and early follicle cells blocks germ cell differentiation and results in defects in cyst encapsulation by follicle cells [9••, 10, 11]. Similarly, ecdysone signaling in the *Drosophila* testes regulates the proliferation and self-renewal of cyst stem cells, indirectly affecting the maintenance of GSCs [13••]. The differential downstream

activation of steroid hormone targets in distinct cell types appears to be a critical determinant of stem cell fate and daughter cell differentiation.

Regulatory Themes and Future Directions

The mechanisms of ecdysone signaling in *Drosophila* are well characterized and largely functionally conserved relative to those of mammalian steroid hormones [34••, 36, 63]. Studies on ecdysone signaling in the *Drosophila* GSC lineage can therefore serve as a guide for the investigation of the role of other steroid hormones in mammalian stem cells. Based on our current knowledge of how ecdysone controls GSCs, we can identify three major challenges for future research.

Identification of Steroid Hormone Target Cells One of the most challenging problems continues to be the identification of relevant cellular players. Which stem cells receive steroid hormone signals directly? What other cell types relay hormonal signals to stem cells? What signal does each cell type receive, and how are direct and indirect signals integrated to control stem cells and their progeny? For example, steroid hormone signaling appears to regulate *Drosophila* GSCs through both cell autonomous and non-autonomous mechanisms. Ecdysone acts directly on GSCs to modulate BMP signaling in GSCs via a functional interaction with the ATPase-dependent chromatin remodeling complex nucleosome remodeling factor (NURF), to control their self-renewal [8]. Ecdysone signaling also indirectly controls GSC maintenance by acting on adjacent somatic cells; however, the molecular mechanisms have yet to be described [10, 11, 43••]. Recent evidence suggests that mouse hematopoietic stem cells directly respond to estrogen via estrogen receptor alpha [17•]. In contrast, mammary stem cells lack estrogen and progesterone receptors but are exquisitely sensitive to steroid hormone signaling [64, 65]. In this case, progesterone and estrogen signal to adjacent luminal epithelial cells, stimulating the production of Wnt4 and RANKL (a signaling molecule upstream of NFκB), which in turn signal to mammary stem cells to promote self-renewal and proliferation [15, 16]. Estrogen and androgen also regulate muscle satellite cells, indirectly promoting their self-renewal and long-term proliferation by upregulating Notch/Delta signaling in myofibrils [18•]. Thus, in the *Drosophila* GSC, the muscle satellite cell, and the mammary stem cell, steroid hormone signaling interacts with local paracrine signals to control stem cell function. This makes the identification of steroid-responsive cells challenging, as traditional gene knock-out approaches for steroid receptors may yield complex phenotypes due to effects in both stem cells and support cells. It is more accurate to envision stem cells as responsive to a complex signaling environment, encompassing both paracrine and endocrine signals that interact among themselves, rather than each signal functioning independently. Given the complexity of steroid hormone signaling, and the extensive cross-talk between stem cells and other surrounding cells, identifying the key cellular players in tissues maintained by stem cells will be a cell type- and tissue-specific proposition.

Elucidation of the Effects of Other Nuclear Hormone Receptors on Stem Cells Steroid hormone receptors, such as EcR and Usp in *Drosophila*, belong to the evolutionarily conserved nuclear hormone receptor superfamily of transcription factors [63, 66, 67]. Nuclear hormone receptors share a common structure with two major domains: a ligand binding domain and a highly conserved DNA binding domain. This unique structure, coupled with their ability to bind a variety of distinct small molecules, including fatty acids, vitamins, and nitric oxide, allows nuclear hormone receptors to directly affect gene expression in response to the concentration of their ligands in the target cell [66–69]. They are thus widely required in both *Drosophila* and mammals for development, reproduction, and metabolism [67]. Although nuclear hormone receptor function has been characterized in many adult tissues, we have only recently come to appreciate the importance of this diverse superfamily in the control of tissue-resident stem cells [3]. For example, Beyaz and colleagues identified peroxisome proliferator-activated receptor-δ (PPAR-δ) and its heterodimeric binding partners liver/retinoid X receptor (LXR/RXR) as mediators of fatty acid-induced enhancement of intestinal stem cell proliferation and self-renewal, despite evidence that PPAR-δ is dispensable for normal intestinal stem cell function [20•]. Another example is the nuclear receptor Tailless (TLX), which is directly required for the maintenance and proliferation of mammalian neural stem cells [70]. Gene knockout approaches in mammals for other nuclear hormone receptors, such as the retinoic acid receptor, have yielded mixed results, possibly due to considerable functional redundancy between receptors [71]. Indeed, the number of duplications in the nuclear hormone receptor superfamily makes defining functional roles in stem cells a challenge requiring sophisticated techniques for manipulating gene function. In this respect, *Drosophila* may be a prime organism in which to explore stem cell-specific roles for nuclear hormone receptors: while there are 48/49 (human/mouse) mammalian nuclear hormone receptors, there are only 18 encoded in the *Drosophila* genome, representing all of the mammalian subfamilies. *Drosophila* thus offer considerably less functional redundancy but evolutionarily conserved physiological functions [63].

Approximately half of the nuclear hormone receptors were identified based on primary sequence homology and have no known ligand. The existence of these so-called orphan nuclear hormone receptors suggests that many signaling molecules and pathways still remain to be identified. Indeed, although the first nuclear hormone receptors were isolated based on the

binding properties of known steroid hormones, recent studies have suggested that some nuclear hormone receptors, particularly lipid-sensing receptors, are activated by a variety of different ligands, making it challenging to identify the primary endogenous ligand [68, 69]. Of note, in *Drosophila*, many orphan nuclear hormone receptors function interdependently with ecdysone signaling [36, 63]. Several EcR target genes encode nuclear hormone receptors, such as *ftz transcription factor 1* (*ftz-f1*) and *Hormone receptor 3* (*Hr3*, also known as *Hr46*), and are key components of the ecdysone-inducible gene network originally identified in the context of larval development [63]. One possibility is that other nuclear hormone receptors might serve as "partner" transcription factors to reinforce or refine the ecdysone signal in specific cell types, such as stem cells or their progeny, by co-regulating common gene targets. For example, during *Drosophila* embryonic and larval development, maximal induction of the EcR targets *E74* and *E75* requires the activity of Ftz-f1 [72–75]. Further, the ecdysone-responsive orphan nuclear hormone receptor *ecdysone-induced protein 78C* (*E78*) genetically interacts with *EcR* to control the growth and survival of germline cysts developing outside of the germarium, although the underlying molecular mechanisms remain unclear [51••]. Future studies testing the function of nuclear hormone receptors in stem cells and their progeny are thus likely to reveal an expansive gene regulatory network.

Identification of Steroid Hormone-Responsive Gene Networks Recent work in *Drosophila* using genome-scale approaches to identify ecdysone-responsive genes has reinforced the hypothesis that steroid hormone signaling promotes distinct gene expression signatures in different cell types [76, 77•, 78]. Moving forward, it will be important to keep in mind that cells in different stages of differentiation, at distinct points in the cell cycle, or in varying microenvironments may have unique, although overlapping [12••], molecular networks. One example can be found in initial studies on ecdysone and cell proliferation in different cellular contexts. There is evidence to support direct regulation of cell cycle genes such as *E2f1* and *cyclin E* by ecdysone [79]; however, other studies have shown that ecdysone signaling also controls cell cycle genes indirectly, for example by upregulating a transcription factor that suppresses Wnt signaling [80], or by promoting changes in glucose metabolism that accompany cell cycle exit and terminal differentiation [14•].

There is also emerging evidence to suggest that ecdysone signaling controls stem cell self-renewal by broadly enhancing the production of intrinsic factors necessary for gene regulation. Genome-wide surveys of ecdysone-responsive genes have found a large number of targets integral for RNA splicing, alternative start site usage, transport, and stability [77•, 78, 81, 82]. Indeed, our own recent work identified the heterogeneous nuclear ribonucleoprotein *Hrb27C* as a key regulator of GSC self-renewal downstream of ecdysone signaling [12••]. One possibility is that ecdysone signaling transcriptionally activates RNA-binding proteins whose function is to regulate transcripts that promote the stem cell fate and suppress differentiation. Ecdysone is also well-known to function with a variety of chromatin remodeling factors and epigenetic regulators, which may change the subset of genes available for expression by modulating chromatin accessibility [36]. These mechanisms are elegant ways to broadly impact gene expression by directly regulating only a limited number of gene targets in a given cell. Identifying the full complement of steroid hormone targets in a given stem cell will thus help us to answer important unresolved questions in stem cell biology, such as the molecular mechanisms controlling the cell cycle, cell metabolism, and cell fate.

With the advent of genomic approaches to study cellular function, we are on the verge of being able to identify networks of hormone-responsive genes that may promote crosstalk between paracrine and endocrine signals to fine tune cell function. Whole-genome analyses such as RNA-sequencing and chromatin immunoprecipitation followed by sequencing will be helpful for identifying key nodes in gene networks. More sophisticated approaches to identifying gene networks at a single-cell resolution in vivo will also help us to generate new hypotheses about molecular control. These approaches, however, must continue to be coupled with traditional genetic functional analyses to fully elucidate complex stem cell controls on a per-cell basis in the context of the physiology of the organism as a whole. Moreover, the complex nature of steroid hormone signaling demands that we carefully examine genetic and functional interactions between different targets or receptors as pieces of a larger gene regulatory network controlling stem cell fate and function.

Relevance of the Hormonal Milieu to Anticancer Therapy and Regenerative Medicine

The evidence demonstrating that undifferentiated cells, including stem cells and precursor cells, respond to complex combinations of hormonal signals has broad implications to our understanding of human disease. Epidemiological data show strong correlations between altered states of physiology, such as obesity, and tumorigenic transformation: indeed, it is estimated that the majority of human cancers arise due to diet or environmental factors rather than genetic factors [83–86]. Many cancers are thought to arise from a modified tissue-resident stem cell or by transformation of a differentiated cell into a proliferative, long-lived, self-renewing "cancer stem cell" [5, 87, 88]. The cancer stem cell hypothesis proposes that the cellular heterogeneity within tumors arises due to the presence and activity of cells that have qualities mimicking those of tissue-resident stem cells [89]. Regardless of the exact nature of the cancer stem cell, several recent studies suggest

that, similar to tissue-resident stem cells, cancer stem cells also sense and respond to steroid hormone signals. In hepatocellular carcinoma, cancer stem cell self-renewal is promoted by thyroid hormone [90]. Breast cancer stem cells, like mammary stem cells, receive hormonal signals through paracrine mechanisms, as they typically do not express either estrogen or progesterone receptors [91]. PPAR-δ-mediated self-renewal of intestinal stem cells also enhances intestinal tumorigenesis [20•]. Since steroid hormone signaling in and around tissue-resident stem cells is clearly complex, additional studies aimed at understanding the molecular underpinnings of steroid hormone responses will likely inform clinical investigations toward more effective cancer therapeutics.

The discovery of induced pluripotent stem (iPS) cells has invigorated the prospects of cell/tissue transplantation and regenerative medicine as potential options for the treatment of many diseases [92, 93]. In principle, de-differentiation of patient-specific skin cells might obviate the need for prolonged immunosuppressant therapy and the risks of graft rejection. Transplantation of specific cell types (as is the case for replacing β cells in diabetics) generated in vitro from iPS cells, however, is still hindered by our limited knowledge of the full complement of factors and epigenetic signatures necessary to coax iPS cells to properly differentiate into a specific terminal fate [94]. Initial transplantation trials for diabetes ameliorated symptoms in rodents by using naive lineage-restricted cells and allowing differentiation to proceed in the graft post-transplantation; however, since it remains unclear what factors are influencing terminal differentiation [95, 96], it is possible that the hormonal physiology of the transplant recipient might play a role. Indeed, a recent study illustrates this important caveat: transplantation into diabetic mice with hypothyroidism can impede the success of the transplant [97]. This finding suggests that hormones can not only affect endogenous stem cell populations but also affect iPS-derived transplanted cells, potentially shaping their ability to self-renew or to effectively generate the terminally differentiated cell population of interest. As clinical approaches are steered progressively toward personalized medicine, the effect of steroid hormones, in particular the sex steroids [98], on regenerative and cancer therapies should not be overlooked.

Conclusions

Steroid hormones control virtually every aspect of human physiology, and the hormonal environment continually changes over the lifetime of the organism. Tissue-resident stem cells are sensitive to steroid hormones and other systemic factors via nuclear hormone receptor signaling, both directly and via hormone-responsive intermediate cells. Hormonal signaling broadly impacts gene expression transcriptionally and post-transcriptionally, through diverse subsets of target genes, including RNA binding proteins and chromatin modulators. While we may have identified a few key intrinsic self-renewal genes modulated by hormones, it is likely that broad networks of genes integrate cell fate and cell cycle progression with physiology. Going forward, elucidating the mechanisms of hormonal control of stem cell fate and function will require sophisticated genetic manipulations. Nuclear hormone receptors employ multiple cellular modes of action, integrating a cell-intrinsic gene regulatory network with other hormones and signals from intermediate cells or tissues, each with their own network of gene expression. The ability of these hormonal networks to rapidly sense and respond to changes in the external environment or in physiological processes allows them to finely modulate stem cell lineages, thereby serving as powerful mediators of organismal adaptation to perpetually changing conditions.

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Compliance with Ethical Standards

Conflict of Interest Elizabeth T. Ables and Daniela Drummond-Barbosa declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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