Molecular and Cellular Endocrinology 288 (2008) 1–5

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Discussion

Commonalities in the endocrinology of stem cell biology and organ regeneration

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ARTICLE INFO

Keywords:
Stem cell
Progenitor cell
Niche
Microenvironment
Organ
Regeneration
Tissue engineering
Regenerative medicine

'If it is not broken, do not try to fix it' is an adage that lauds the occasional virtue of inactivity. However, for most, if not all, of the human body's organs and tissues there is no such rest. All of the two hundred plus different cell-types within the human body constantly require careful attention to maintain optimal function. The longevity of our lives, far greater than the lifespan of most single cells, brings with it a requirement for continual tissue and organ regeneration, where cell loss is perfectly matched by cell replacement; continual 'breaking' that necessitates 'fixing' on a day-to-day, month-to-month and year-to-year basis. This issue of *Molecular & Cellular Endocrinology* examines the mechanisms underlying this process for a range of organs, both in health and disease coupled to the potential for selected cell replacement therapies.

The project set out with the goal of bringing together a range of articles examining the role of hormones and growth factors on stem or progenitor cells and their progeny in endocrine organs and other hormone-relevant sites (Table 1). The result is 10 articles (Berry et al., 2008; Gargett et al., 2008; Garrett and Emerson, 2008; Gray, 2008; Hanley et al., 2008; Hoffman, 2008; Ishizuya-Oka and Shi, 2008; Kristensen et al., 2008; Paus et al., 2008; Rowland and Brubaker, 2008) that should be considered alongside a previous review in *Molecular & Cellular Endocrinology* on the regeneration of the adrenal cortex from resident stem cells (Kim and Hammer, 2007). To complement these in vivo paradigms, three examples are included here of current in vitro stem cell work aiming to generate terminally differentiated cell-types for clinical therapy (Best et al., 2008; Moore et al., 2008; Tare et al., 2008): an endocrine twist on cell therapy meets regenerative biology. The outcome underlines mechanistic themes with the potential for new research driven by extrapolation across otherwise distinct locations. One emergent thread running through many of the articles is the critical importance of microenvironment—the 'niche', comprised of stem or progenitor cells in vascularised biological matrices that respond selectively to a range of intercellular signals depending upon, amongst other factors, cell receptor expression. Correct assembly of the niche permits healthy organs and tissues that continually regenerate without scarring, and offers the blueprint for ex vivo tissue engineering. Other articles describe dysplastic or aberrant construction as a potentially causative factor in a range of disorders and diseases from epilepsy to cancer.

In some locations, such as the central nervous system (CNS) (Gray, 2008) and pancreas (Hanley et al., 2008), the presence of clearly defined adult stem cells or progenitors remains contentious. However, for these organs it is still possible to discern microenvironments, either in situ or once cells have been taken in vitro, where a regenerative capacity seems feasible. Here, author teams have been encouraged to speculate on potential as well as proven mechanisms. In other locations such as the intestine (Rowland and Brubaker, 2008), testis (Hoffman, 2008) and skin (Paus et al.,

Abbreviations: PTH, parathyroid hormone; HSC, haematopoietic stem cell; IGF, insulin-like growth factor; PTHrP, PTH-related peptide; FGF, fibroblast growth factor; ESC, embryonic stem cell; GLP, glucagon-like peptide; T3, triiodothyronine; TR, thyroid hormone receptor; SHH, sonic hedgehog; BMP, bone morphogenic protein; MMP, matrix metalloproteinase; IGFBP, IGF-binding protein; ER, estrogen receptor; GFP, green fluorescent protein; MSC, mesenchymal stem cell; SSC, spermatogonial stem cell; GCT, germ cell tumour; GDNF, glial cell line-derived neurotrophic factor; CIS, carcinoma-in-situ; EC, embryonal carcinoma; NPY, neuropeptide Y.

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0303-7207/$ – see front matter
doi:10.1016/j.mce.2008.04.001

Table 1
Definitions and a summary of the organ regeneration covered in this issue

Definitions			
Stem cell		Long-term self-renewal combined with the ability to give rise to differentiated cell-types	
Progenitor cell		Limited or no capacity for self-renewal but an ability to give rise to differentiated cell-types	
Location	Stem cell	Supportive evidence	Reference for this issue*
Bone marrow	**Haematopoietic stem cell**	**Regular renewal of blood cells and the success of bone marrow transplantation**	Garrett and Emerson (2008)
	Mesenchymal stem cell	Ability to form cartilage, bone, muscle and fat but precise characterization of the underlying stem cell phenotype remains debated	Tare et al. (2008)
Intestine	**Intestinal epithelial stem cell**	**Regular renewal of gut epithelium**	Rowland and Brubaker (2008)
Skin/hair follicle	**Epithelial stem cell**	**Regular renewal of skin and the success of skin grafting**	Paus et al. (2008)
Testis	**Spermatogonial stem cell**	**Regular production of sperm and transplantable stem cell populations**	Hoffman (2008)
	Carcinoma in situ stem cell	Emerging concept that stem cells underlie germ cell tumours	Kristensen et al. (2008)
Adrenal gland	Adrenocortical stem cell	Ability to repopulate the different adrenocortical cell-types from very few precursor-like or possibly true subcapsular stem cells	Kim and Hammer (2007)*
Brain	Hippocampal stem cell	Emerging evidence that the CNS is not comprised of entirely post-mitotic cells and that stem cell activity may underlie critical aspects of brain function	Gray (2008)
Uterus	Epithelial and stromal stem cells	Monthly menstrual cycle with endometrial renewal	Gargett et al. (2008)
Prostate	Prostate stem cell/prostate cancer stem cell	The emerging concept that stem cells underlie prostate cancer	Berry et al. (2008)
Pancreas	Adult beta cell stem cell	Highly contentious but evidence that ductal or periductal cell populations retain an ability to re-initiate beta cell differentiation	Hanley et al. (2008)

Bold type is used for proven adult stem cell populations. References to associated articles in this issue are listed plus one (*) from a preceding issue of *Mol Cell Endocrinol*.

2008), the presence of true adult stem cells is established (listed in bold type in Table 1). In this setting, authors have included the potential for endocrine and growth factor regulation that has previously been largely unscripted. A beautiful example is the regulation of haematopoiesis by parathyroid hormone (PTH) signalling (Garrett and Emerson, 2008). Historically, those interested in bone, in rheumatology or orthopaedics, have ignored the organ's role in making blood from its central marrow spaces—the preserve of haematologists. Of course, arbitrarily dividing clinical specialties is biological nonsense and with bone and blood production juxtaposed perhaps it should be expected that the major hormone orchestrating the deposition and resorption of bone by osteoblasts and osteoclasts should also turn out to regulate the haematopoietic niche. It transpires that PTH signals through the osteoblast, at least in part via the local production of insulin-like growth factor-1 (IGF1), to increase the number of haematopoietic stem cells (HSCs) resident in the marrow spaces (Calvi et al., 2003). The consequences are fascinating and provoke questions about similar cell signalling in other niches around the body. For instance, is there a similar microenvironment during gestation when PTH-related peptide (PTHrP) is more prevalent than PTH but signals through the same cell surface receptor? Similarly, during gestation where fetal haematopoiesis predominates in the liver, is IGF2 more important than IGF1, recognizing that both hormones can act via the type 1 IGF receptor (IGF1R)?

Several articles here and elsewhere report IGF signalling as a 'funnel' for diverse inter-cellular communication. Ex vivo, IGF2 has recently been proposed as a major mediator of human embryonic stem cell (ESC) renewal (Bendall et al., 2007); fibroblast growth factor (FGF)-2 stimulating its production by differentiated cells on the periphery of ESC colonies. In this issue, Rowland and Brubaker discuss the role of glucagon-like peptide 2 (GLP-2) signalling in regulating intestinal stem cells and the renewal of the gut epithelium (Rowland and Brubaker, 2008). As with PTH in bone, GLP-2 in gut is proposed to act via IGF1. GLP-1 and GLP-2 are both derived from intestinal L-cells by the action of prohormone convertase 1/3 on proglucagon (Drucker, 2005). Whereas GLP-1 is an incretin, enhancing insulin secretion (Drucker, 2006), GLP-2 is intestinotrophic; increasing mucosal thickness and surface area, and favouring crypt cell proliferation over apoptosis in both the small and large intestine (Brubaker and Drucker, 2004; Drucker et al., 1996). Whether these effects are targeted directly at the intestinal stem cell or include actions on the transit amplifying cells can be anticipated from the next phase of cell-specific gene targeting experiments in mice. In this issue, Ishizuya-Oka and Shi complement the article by Rowland and Brubaker by reviewing the amazing role of thyroid hormone in remodelling the amphibian gut as part of amphibian metamorphosis (Ishizuya-Oka and Shi, 2008). It seemed timely to consider whether insight from this fascinating phase of *Xenopus* development might be beneficial for understanding day-to-day mammalian intestinal renewal. The topic is challenging as the genome-wide tools of microarray and genomic 'ChIP-on-ChIP' arrays, readily available and comprehensive for major mammalian model species, are only just becoming accessible for study of *Xenopus*. It transpires that the gut remodelling in *Xenopus* is most likely via the genomic actions of T3 (Buchholz et al., 2004; Ishizuya-Oka and Shi, 2008). In mice, inactivation of thyroid hormone receptor (TR) α causes underdeveloped intestinal crypts and villi (Plateroti et al., 1999, 2001). Although conjectural, perhaps the common contribution of thyroid hormone signalling across these species is twofold: establishing the appropriate niche for adult intestinal stem cells and then regulating the balance between intestinal epithelial cell proliferation, differentiation and apoptosis. In *Xenopus*, thyroid hormone signalling induces expression of epithelial cell sonic hedgehog (SHH), which promotes bone morphogenetic protein (BMP)-4 release from the sub-epithelial fibroblasts lining