

Stem cell researchers find their niche

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The EuroSTELLS Workshop 'Stem Cell Niches', organised by Anna Bigas, Ernest Arenas and Pasqualino Loi, took place in January 2008 in Barcelona, Spain. The goal of the conference was to promote scientific collaboration and synergy between stem cell researchers worldwide and those in the EuroSTELLS consortia (an initiative of the European Science Foundation EUROCORES Programme), and to stimulate discussion of the latest results in the field of stem cell niches.

Introduction

Stem cell function depends on the interaction between intrinsic genetic programmes and extrinsic regulatory cues derived from a stem cell's microenvironment or 'niche'. The concept of the stem cell niche was initially proposed by Schofield in the context of the mammalian blood system (Schofield, 1978). Thirty years on, the niche concept has been generalised to include many different stem cell systems and is considered to represent a defined anatomical location that preserves stem cells and affords their expansion. The limited availability of stem cells within niches also contributes to how the size of a stem cell compartment is determined. Much current interest and excitement surrounding stem cells and their niches pertains to their potential clinical utility in transplantation and regenerative medicine settings. Stem cells are, however, something of a mixed blessing. For long-lived metazoans, there appears to be an evolutionary trade-off between the regenerative potential of stem cells and their vulnerability to neoplastic transformation. Thus, in many instances, cancer may be a disease of stem or stem-like cells (Reya et al., 2001), and, as we discuss below, this was another key theme of this meeting.

In the niche: from reprogramming to asymmetric divisions

Despite intensive research into stem cells, we still understand little of what defines 'stemness' molecularly. The stunning, recent experiments of Yamanaka and co-workers (Takahashi and Yamanaka, 2006; Okita et al., 2007) have highlighted that stemness, in the context of pluripotency, can be imposed upon mammalian genomes by a relatively modest handful of transcriptional regulators. Cellular reprogramming, whether by cell fusion, somatic cell nuclear transfer or transcription factor transduction, also requires changes at the epigenetic level and thus, the first part of the conference focused on epigenetic regulators and reprogramming.

Manel Esteller [Spanish National Cancer Research Centre, (CNIO), Madrid, Spain] exemplified the scope of epigenetic influence by highlighting the biological variation that is observed between monozygotic twins and cloned animals. He went on to

discuss that numerous microRNA promoters are unmethylated in human ES cells. When ES cells differentiate into different lineages, different sets of microRNA-encoding loci become methylated, providing evidence for the tissue-specific methylation of these loci. Regardless of the particular lineage pathway involved, differentiated human ES cells downregulate sirtuin 1, a histone deacetylase. Its inhibition in human ES cells results in enhanced spontaneous differentiation. Sirtuins might therefore be of therapeutic significance, as they are overexpressed in cancer cells, and sirtuin inhibitors inhibit the development of thymic lymphomas in murine models.

In cell lineage-tracing studies, Thomas Graf [The Centre for Genomic Regulation (CRG), Barcelona, Spain] asked how 'instructive' transcription factors drive lineage choice in blood cells. In his research, Graf has used T lymphocytes to test for the myeloid-instructive capacity of the myeloid-affiliated transcription factor CEBP α . He has found that the expression of CEBP α can reprogramme pre-T cells into functional macrophages. Authentic genome reprogramming occurred in these experiments, as shown by T cell receptor rearrangements in the reprogrammed macrophages and by the expression of a YFP reporter indicative of recombination in a pre-T ancestor cell. Other factors involved in this process, Graf discussed, are PU.1 (also known as SPI1), the deletion of which inhibits reprogramming in this setting, and Notch signalling. Taken together, Graf's studies highlight how transcription factors function in hierarchical networks to specify cell fate and identify pathways that might be used to respecify these cells for clinical or commercial benefit.

Symmetric and asymmetric cell division provides a mechanism for the crucial regulation of stem cell numbers, and Weimin Zhong (Yale University, New Haven, CT, USA) asked whether stem cells use intrinsic asymmetric divisions to achieve this. The asymmetric segregation of Numb (a cytoplasmic signalling protein that functions in asymmetric cell fate in *Drosophila*) is essential for neural stem (progenitor) cells to balance the competing needs of self-renewal and differentiation during mouse neurogenesis (Fig. 1). He showed that the two mouse genes, *Numb* and its homologue *numb-like* (*Numbl*), are functionally redundant. Total loss of both Numb activities results in neural progenitor depletion, caused by an initial overproduction of differentiated neurons. The reintroduction of Numb isoforms with symmetric or asymmetric localisation properties showed that only the asymmetrically distributed form could rescue the *Numb/Numbl* double-knockout phenotype. The symmetrically distributed form does not rescue and the mutant mice die because they produce very few differentiated neurons. Thus, it is the distribution of Numb, not its absolute level, that is critical. Zhong also presented evidence that Acbd3 (cyl-Coenzyme A binding domain containing 3) might function as a Numb partner (Zhou et al., 2007). Acbd3 is involved in the maintenance of Golgi structure and function through its interaction with the integral membrane protein giantin (also known as Golgb1). Since Acbd3 is Golgi-associated, Numb and Acbd3 can only interact when the Golgi fragments during cell division, providing a novel mechanism for the coupling of cell fate determination with cell cycle progression. Numb-mediated asymmetric cell division, Zhong suggested, might therefore be used by stem cell progeny in many tissues, when they choose between self-renewal and differentiation.

Bernd Giebel (Heinrich-Heine University of Düsseldorf, Germany) reported that upon cultivation, human primitive

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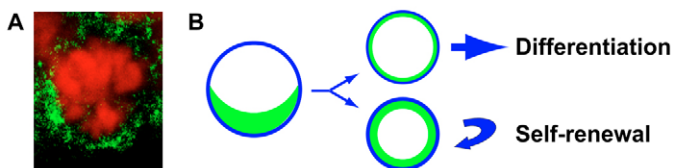


Fig. 1. Asymmetric Numb segregation enables neural stem cells to balance self-renewal and differentiation during mouse neurogenesis.

Mammalian Numb proteins localise to one side of the cell membrane in dividing neural stem (progenitor) cells and can be differentially inherited by the two daughter cells. (A) An immunofluorescent neural stem cell with Numb protein (green) localised asymmetrically. Red fluorescence indicates the chromosomes. (B) Schematic of a neural stem cell and its daughter cells, showing the localisation of Numb (green; apical localisation is shown in the neural stem cell). The daughter cell that inherits the most Numb self-renews, whereas the one that inherits less Numb becomes a neuron. Images courtesy of Weimin Zhong.

haematopoietic stem/progenitor cells (HSC/HPCs) acquire a polarised morphology and redistribute different lipid-raft-associated antigens mainly to either the leading edge or the uropod. This polarity is maintained in dividing HSC/HPCs. Giebel's team further identified four different antigens [CD53, CD62L (SELL), CD63 and CD71 (TFRC)] that segregate asymmetrically in ~20% of HSC/HPCs studied. Since CD53, CD63 and CD71 are linked to the endosomal compartment, his group have shown both that HSC/HPCs can divide asymmetrically and that a link exists between asymmetric cell division and the endosomal compartment.

Malignant stem cells and their niches

According to the cancer stem cell hypothesis, the cell hierarchies in cancer resemble those in normal tissues. Cancer stem cells spawn the more-differentiated cells that account for most of a tumour. As such, the bulk of a tumour lacks significant self-renewal capacity and is thus unable to maintain or to reinitiate cancer in experimental models or in relapsed patients. Although a popular view, the cancer stem cell hypothesis is not unchallenged and its validity has been recently debated (Kelly et al., 2007). Thus, it was with interest that the conference learned of breaking developments in cancer stem biology.

The identification and characterisation of cancer stem cells is most advanced in the leukaemias, particularly in adult myelogenous leukaemia (AML). AML cancer stem cells comprise only a small fraction of the leukaemic population and share surface markers with normal haematopoietic stem cells (HSCs). Approximately 9% of de novo AML cases are due to mutations in the C/EBP α transcription factor gene (*CEBPA*) (most commonly affecting the p42 isoform). Claus Nerlov (EMBL, Monterotondo, Italy) has explored AML cancer stem cell biology using a mouse model in which the p42 isoform of C/EBP α has been specifically ablated. His results indicate that committed haematopoietic progenitors can function as cancer stem cells in AML through the action of distinct initiating mutations.

Tariq Enver (Oxford University, Oxford, UK) has explored cell hierarchies in paediatric acute lymphoblastic leukaemia (cALL), the commonest childhood cancer. Rare cells within cALL samples, which display a mixed stem/B-cell phenotype, comprise the self-renewing cancer stem cell compartment. But how does the cancer start? Such issues can only be addressed with access to the pre-cancerous state, which in cALL is clinically silent. Towards answering this question, Enver presented recent insights into the pre-cancerous stages of cALL gained from monozygotic twins (Hong

et al., 2008). During their development in utero, one twin developed a pre-cancerous cell clone that spread to the other twin via their shared placental circulation. Variability in their acquisition of additional mutations led to one twin presenting with cALL, whereas the other was haematologically normal. Analysis of the healthy twin revealed the presence of pre-cancerous cells with a mixed stem/B-cell immunophenotype and stem cell-like characteristics. The discovery of these pre-leukaemic stem cells will allow their biological properties to be explored and will inform research into how 'second hits' are generated and contribute to leukaemogenesis.

Tsvee Lapidot's (Weizmann Institute, Rehovot, Israel) studies of the regulation of normal haematopoietic niches in mice highlighted just how dynamic the niche is. He reported that apparently neutral procedures, such as minor bleeding, result in major changes in the prevailing regime of extrinsic regulators and cell-cell interactions in the niche microenvironment. Thus, we should expect complexity as we explore the role of the niche in the regulation of cancer stem cells. As alluded to by Lapidot, niche-dependent mechanisms of cancer stem cell regulation might provide novel targets for therapeutic intervention.

Several studies focused on the role of developmental signalling pathways [Hedgehog (Hh), Bone morphogenetic protein (BMP), Notch and Wnts] in the biology of other tumours. Ariel Ruiz i Altaba (University of Geneva, Geneva, Switzerland) discussed the essential role of Hh-Gli signalling in stem cells and cancer stem cells. He presented a new mouse model in which *Gli1* expression can be induced in the mouse brain, resulting in increased neural stem cell numbers. He also showed that Hh-Gli signalling is essential for the self-renewal and proliferation of human glioma cancer stem cells (Clement et al., 2007), as well as for the sustained expression of genes that form a 'stemness' signature, such as *NANOG*, *nestin*, *BMI1* and *SOX2*. Gli function thus appears to be crucial for determining stem cell numbers and possibly the behaviour of cancer stem cells. Specific inhibitors of Hh-Gli function might thus provide the basis to combat multiple cancers.

The role of the Notch and Wnt signalling pathways in colorectal cancers (CRCs) and in intestinal crypt stem cells (see Fig. 2) was also discussed at this meeting. Eduard Batlle (Institute for Research in Biomedicine, Barcelona, Spain) explored the more mechanistic aspects of CRC development, focusing on the role of EphB-ephrin B interactions. As is well known, activating mutations in Wnt signalling are involved in CRC formation. EphB2 and EphB3 tyrosine kinases are downstream targets of this signalling pathway. These proteins control intestinal epithelial architecture through repulsive interactions. Batlle discussed how, in EphB mutant mouse models, the loss of EphB expression accelerates tumourigenesis in the colon of mice with activated Wnt signalling. Notch signalling also plays an essential role in Wnt-mediated tumourigenesis in the intestine. However, the mechanism leading to Notch activation in this type of tumour and the specific contribution of Notch remain unknown. Lluís Espinosa [Bellvitge Institute for Biomedical Research (IDIBELL), Barcelona, Spain] presented data demonstrating that jagged 1 is a transcriptional target for β -catenin in CRC cells.

Signalling in the adult and embryonic haematopoietic niche

HSCs were the first identified, and are therefore the most studied, adult stem cell. For over 50 years, these stem cells have been used in clinical therapies for leukaemias and blood-related diseases. Yet our knowledge of how they expand and self-renew and of the molecules that support their maintenance and retention in the niche is limited.

Results from Liheng Li's (Stowers Institute, Kansas City, MO, USA) laboratory show that HSCs are juxtaposed to N-cadherin⁺ osteoblastic cells in the endosteal niche of the marrow of the long bones. Much of his talk focused on the role of N-cadherin on HSCs in the niche and during their homing. He drew parallels to neural crest cells, as they undergo dynamic changes in N-cadherin expression during their migration. Consistent with the reduced levels found on migrating neural crest cells, Li found that actively homing and mobilised HSCs express low levels of N-cadherin. His data also indicate that two pools of adult HSCs exist: a pool of N-cadherin-intermediate-expressing cells that are quiescent and stably adhere to the niche; and the N-cadherin-low-expressing primed HSCs, which are more active in entering the cell cycle. Intriguingly, HSCs with intermediate and low levels of N-cadherin might predominantly associate with the endosteal and vascular niches, respectively.

Tsvee Lapidot also focused on the mechanisms and molecules that regulate HSC homing, motility and retention in the bone marrow. Osteoclast/osteoblast bone remodelling frees stem cells from their adhesion interactions with the endosteal niche, inducing their mobilisation into the circulation. Interactions between the chemokine SDF1 (now known as CXCL12) and its receptor CXCR4 play a major role in this process. The secretion of SDF1 by bone marrow stromal cells is essential for the egress of progenitor cells. This process is intensified and amplified by neurotransmitters, by SDF1 itself and by the CXCR4 antagonist AMD3100, which all lead to increased SDF1 secretion by CXCR4-positive bone marrow stromal cells, followed by rapid mobilisation, often of immature cells.

The Notch signalling pathway was a focus of the discussions about HSC development. Raphael Kopan (Washington University, St Louis, MO, USA) described recent insights gained from the study of the NIP-Cre mouse, in which cells experiencing Notch1 activation are marked. This analysis failed to reveal a common theme for Notch1 activity in the various adult stem cell compartments studied. In the epidermis, Notch1 activation promoted stem cell exit from the niche; in the intestine, it played a redundant role with Notch2; and its activity in aortic endothelial cells made it difficult to ascertain whether Notch1 was required specifically in the definitive HSC or for the emergence of its haemogenic endothelial progenitor. However, data presented by Anna Bigas (IDIBELL, Barcelona, Spain) strongly implicated a role for Notch1 signalling in HSC fate determination in the aortic endothelium. Her analysis of jagged 1 (a Notch ligand)-deficient mouse embryos revealed a complete absence of Gata2-expressing cells (HSCs and endothelium) and a decrease in functional haematopoietic progenitors. Her chromatin immunoprecipitation analysis showed that Notch1 binds to the *Gata2* promoter. Together, these data strongly suggest that Notch1 signalling is involved in lateral inhibition and in haematopoietic fate determination in the embryonic dorsal aorta. Notch also appears to be involved in HSC maintenance at later stages of development, as discussed by Urban Lendahl (Karolinska Institute, Stockholm, Sweden). He reported that during hypoxia, the hypoxia-inducible transcription factor HIF1 α is more effectively recruited to hypoxia-induced promoters when Notch is active. The physiological relevance of this is underscored by the fact that HSC niches, at the endosteal surfaces of trabecular bone and in the vascular sinuses, are known to be hypoxic and that stem cells rapidly become exhausted when exposed to oxidative stress.

Roger Patient (Oxford University, Oxford, UK) provided a wider view of developmental signalling in the niche during the onset of haematopoiesis in the zebrafish dorsal aorta. He showed that the initiation of the HSC programme, like the endothelial programme, requires Hh, VEGF and Notch signalling. Subsequently, Hh protein

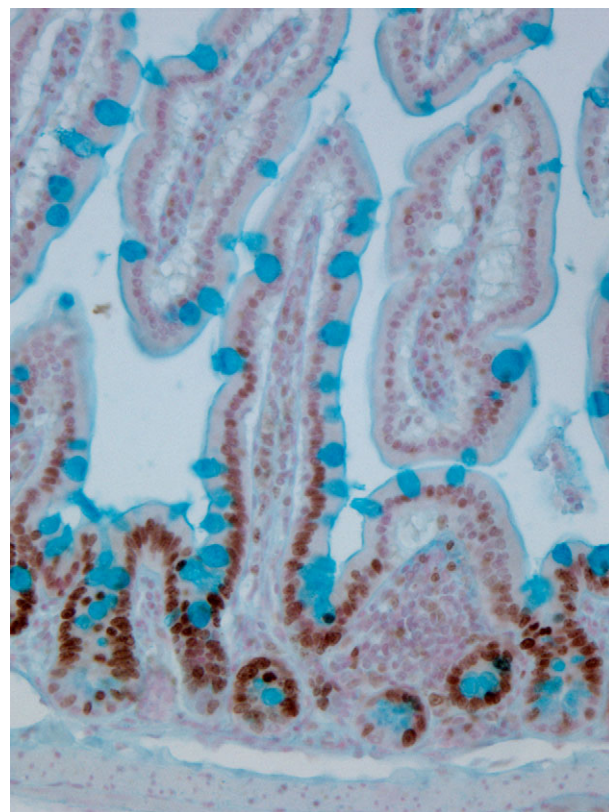


Fig. 2. Proliferation and differentiation in mouse small intestine.

The proliferating compartment of an intestinal crypt of an adult mouse small intestine, as revealed by Ki67 immunohistochemistry (brown), which stains proliferating cells, and Alcian Blue staining, which detects mucosecretory differentiated cells. Image courtesy of Verónica Rodilla and Lluís Espinosa.

emanates from cells dorsal to the aorta and BMP (Bmp4) from cells ventral to the aorta. To determine how HSCs are induced within the ventral aortic endothelium, the aortic floor was exposed to continued Hh signalling using an agonist. Arterial marker expression characteristic of the aortic roof was induced, but the HSC programme was not suppressed. Suppression of the HSC programme required the inhibition of BMP signalling with a heat shock-inducible dominant-negative BMP receptor. Thus, these morphogens polarise the aorta, leading to HSC production only in the floor. Elaine Dzierzak (Erasmus University, Rotterdam, The Netherlands) presented dorsal-ventral positional studies of the mouse embryonic aorta. She showed in an explant culture system that HSC numbers in the aorta increase when ventral tissues are included in the culture and that HSC numbers decrease in the presence of dorsal tissue. When Hh protein is added to AGM (aorta-gonad-mesonephros region) cultures, HSC numbers increase, indicating that Hh is a positive regulator of HSC regulation, in contrast to the results in the zebrafish. Dzierzak also discussed the importance of BMP signalling in the ventral aortic region and for HSC growth, and suggested that BMP emanating from mesenchymal cells interacts with the adjacent ventral aortic haemogenic endothelium (Durand et al., 2007).

The neurogenic niche

Central nervous system (CNS) development is a highly complex process, and several talks highlighted the intricate relationships that exist between a local niche and extrinsic signals during the

regulation of adult neurogenesis. Of particular interest to the participants were the presentations on the signalling events that lead to the patterning, cell fate determination and establishment of self-renewing stem cell populations in the brain.

During a one-week period of mouse embryonic life, neural stem cells (NSCs) first divide symmetrically to expand the lateral dimensions of the cortical ventricular zone, then asymmetrically to generate neurons, which drive the expansion of the radial dimension of the cortex. Although it has been speculated that a secreted signalling molecule regulates this switch from symmetric to asymmetric division, its identity remains elusive. Sam Pleasure (University of California, San Francisco, CA, USA) focused on this issue in the prenatal mouse cortex. He presented strong evidence that the mesenchymal covering of the brain, the meninges, is the source of a required component of this signal. Pleasure showed that mice that do not properly produce meninges fail to make this cell division switch appropriately. Instead, they continue to expand their neuroepithelium laterally at the expense of neuron production. Using a slice explant system, his laboratory has shown that a soluble signal from the meninges is responsible for this activity; this signal's identity is eagerly anticipated.

Known developmental signalling molecules, such as Wnt, BMP, Shh and Fgf8, are expressed during mouse neurogenesis and appear to play a role in the highly regulated patterns of cell division and differentiation. Wnt and BMP are involved in dorsal forebrain patterning, whereas Shh is involved in ventral patterning. Fgf8 appears to be involved in anterior patterning. At E11, neurons begin to appear in the cortex, developing in the well-described 'inside-out formation'. Radial glial cells are anchored at one pole in the ventricular zone and at the outer end pole to guide neuron migration. As discussed by Ondrej Machon from Stefan Krauss' laboratory (Norwegian Center for Stem Cell Research, Oslo, Norway), during mouse telencephalon development, Wnt signalling is normally restricted dorsally. The initiation of the neurogenic programme [characterised by the expression of *Meis2*, *Pax6*, *Ngn2* (*Neurog2*) and *Tbr2* (*Eomes*)] occurs as canonical Wnt signalling retreats in a lateral-to-medial and anterior-to-posterior direction. To examine whether this dynamic Wnt gradient is of biological significance to neural development, Machon analysed several Cre-lox recombination models. His results show that maintained canonical Wnt signalling delays the onset of the neurogenic programme. By contrast, the deletion of β -catenin accelerated the neurogenic programme. β -catenin dosage was also implicated in the specification of area identity in the lateral cortex. Here, sustained Wnt signalling yielded hippocampal-like cells in the cortical plate and dentate gyrus-type cells in the hippocampus.

Magdalena Goetz (GSF Institute of Stem Cell Research, Neuherberg, Germany) presented new data on the neurogenic role of BMP in the lateral ventricle, one of the two neurogenic niches in the adult mouse brain. She showed that BMP-mediated signalling is active in this neurogenic zone exclusively in astrocytes/stem cells. After conditional deletion of *Smad4*, or following noggin infusion, neurogenesis was severely impaired in adult NSCs. Most strikingly, the progenitors then reverted to the generation of oligodendrocytes. This was due to the upregulation of the transcription factor Olig2. A dominant-negative construct of Olig2 fully rescues the phenotype and restores neurogenesis. Thus, BMP signalling in the neurogenic niche serves to suppress Olig2 and the acquisition of oligodendrocyte fate, which is the default fate of progenitors outside the neurogenic niches. Consistent with this scenario, suppression of Olig2 function outside the neurogenic niches results in the activation of some neurogenic factors and the initiation of neurogenesis.

Continuing with TGF signalling and its implications for stem cell self-renewal and differentiation, Danny Huylebroeck (University of Leuven, Leuven, Belgium) discussed the fine-tuning and selectivity roles provided by Smad-interacting proteins (SIPs). Huylebroeck showed Sip1 to be of particular importance during central (forebrain, including corticogenesis) and during peripheral (neural crest-derived dorsal root ganglia) nervous system development. He also reported that Sip1-deficient ES cells, which offer a new system in which to study Sip1, fail to differentiate into neurons and astrocytes in monodifferentiated cell cultures.

Of course, the long-term goal of many brain developmental studies is to treat neurological disease. Experimental therapies with mesencephalic dopaminergic (DA) neurons have offered some promise for treating Parkinson's disease. Ernest Arenas (Karolinska Institute, Stockholm, Sweden) reported how Wnt5a regulates the differentiation of DA precursors to DA neurons in the mouse midbrain. When NSCs derived from the ventral midbrain were cultured as neurospheres, manipulated to overexpress Wnt5a and transplanted in vivo, they contributed to the behavioural recovery of Parkinsonian mice. These cells were properly integrated and electrophysiologically normal. These results, together with the improved growth of DA neurons in Wnt5a-supplemented human ES cell differentiation cultures, hold promise for future clinical application. Another movement disorder, Huntington's disease (HD), is characterised by the specific degeneration of striatal projecting neurons. Thus, in vitro stem cell differentiation directed towards this fate would aid cell-replacement strategies for treating HD. Josep M. Canals (University of Barcelona, Barcelona, Spain) presented data on the Ikaros transcription factor, which is necessary for the neurogenesis of striatal projecting neurons. Findings from his group show that Ikaros is necessary but not sufficient to direct stem cell differentiation to the GABAergic phenotype for cell replacement for HD.

The expansion of adult NSCs in culture is also advantageous to cell-replacement approaches. Isabel Farinas (Centro de Investigacion Principe Felipe, Valencia, Spain) focused on the intrinsic and extrinsic mechanisms that regulate self-renewal in adult NSCs of the murine subependymal zone. Her group recently identified the vascular factor Pedf (pigment epithelium-derived factor; also known as Serpinf1) as a self-renewing niche factor for adult NSCs. Pedf regulates symmetrical divisions by enhancing the activity of the Notch pathway through activation of the NF κ B pathway.

More stem cells and more niches

Generally, the stem cells found in many adult vertebrate tissues [such as NSCs, mesenchymal stem cells (MSCs) and HSCs] are restricted in their differentiation potential to the lineages within that tissue. However, a variety of adult multipotent stem cells have been described in the literature. To better understand the position of multipotent adult progenitor cells (MAPCs) in a developmental stem cell hierarchy, Catherine Verfaillie (Stem Cell Institute, Leuven, Belgium) presented transcriptome data obtained from several stem cell types. She demonstrated that MAPCs differ from classical adult multipotent stem cells, such as NSCs and MSCs, in their transcriptome. Interestingly, MAPCs express some (but not all) of the pluripotency genes that are expressed in ES cells and four of the six factors that have recently been reported to reprogramme mouse and human fibroblasts into induced pluripotent stem (iPS) cells, suggesting that this mechanism underlies their potency, although knock-down studies are still in progress to confirm this. Whether these cells exist in vivo or are induced in vitro as a consequence of

long-term culture is still not known. MAPCs appear to also have an early endodermal programme that may be elaborated owing to the fact that they do not express Nanog, a possibility that is being evaluated. Whether that provides information on how far back a MAPC may be de-differentiated, or at what stage of development they have been 'set aside', is not yet known.

The pancreas and its β -islet cells are currently of particular interest in stem cell and regenerative medicine because of their therapeutic application for treating diabetes. Among his findings, Henrik Semb (Lund University, Lund, Sweden) discussed the production of β -cells from human ES cell cultures by the sequential addition of factors such as activin A and FGF4. Bernat Soria (presently the Minister for Health, Spain) presented data from his former laboratory in Seville that show that mouse ES cells that contain a 'lineage trap' (an insulin promoter-driven hygromycin selectable marker) can be differentiated in culture by the addition of conditioned media from embryonic pancreatic buds. The differentiated ES cells express Pdx1, insulin and other islet cell markers. Moreover, after transplantation under the kidney capsule of streptozocin (STZ)-diabetic mice, they restored normal blood glucose levels (Vaca et al., 2006). These studies will inform the production of clinical-grade cells for future therapies.

The skin is the body's primary means of defence against the impinging external environment and is maintained by epidermal stem cells. Salvador Aznar Benitah (CRG, Barcelona, Spain) showed that Rac1 is essential for maintaining mouse epidermal stem cells in a quiescent state and localised to their niche. He showed in mouse models that Rac1 modulates the activity of Myc, which is required for epidermal stem cells to exit their niche by inducing their proliferation and de-adhesion from the extracellular matrix. In this sense, Myc, as in HSCs, allows epidermal stem cells to differentiate, rather than inhibiting their differentiation, as in other adult tissues (such as the mammary gland, pancreas or liver). Rac1 maintains a low activity of Myc in epidermal stem cells by inducing its phosphorylation at three C-terminal residues, which prevents Myc from interacting with its transcriptional partner Max and from binding to its target promoters, thereby preventing its transcriptional activity. Hence, the balance of Rac1 and Myc activities modulates epidermal stem cell maintenance and exit from the niche.

Finally, one of the most accessible and intriguing adult stem cell populations is that of the regenerating vertebrate tooth. Irma Thesleff (Institute of Biotechnology, University of Helsinki, Helsinki, Finland) introduced the stem cell niche in the continuously growing incisor of the mouse, where interactions between the epithelial and mesenchymal tissues regulate the proliferation and differentiation of the epithelial stem cells. These cells are responsible for tooth

growth and replenish the pool of enamel-producing cells. BMP and activin modulate FGF signals in this system, and follistatin regulates the asymmetry of the organ, by acting as an activin inhibitor during proliferation and as a BMP inhibitor during differentiation.

Conclusion

Stem cell scientists certainly 'found their niche' at this conference. The presentations and discussions about stem cell niches in many distinct tissues during development and in the adult provided new insights into how tissues and stem cells are formed and maintained under normal conditions. We learned that niches most likely play a role in disease processes, and affect cancers and cancer stem cells. In the long term, the clinical applications of tissue repair and regeneration will rely both on stem cells and on the complex interactions between multiple cell types that make up a whole tissue. Hence, through extensive scientific investigation, the cellular interactions and molecular players that are of importance in stem cell niches are beginning to come into focus.

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