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Editorial Overview: The ins and outs of stem cells in differentiation, inflammation & disease

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Cédric Blanpain is full professor and WELBIO investigator at the Université Libre de Bruxelles, Belgium. His lab is studying epidermal, prostate and mammary gland stem cells during development, homeostasis and repair. He is also studying the cancer cell of origin in these different tissues, and the role of cancer stem cells during tumor growth and resistance to therapy

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Erwin Wagner obtained his PhD for studies on bacterial genetics in Berlin. He did postdoctoral training with Beatrice Mintz in Philadelphia (1979–83), became Group Leader at the EMBL, Heidelberg (1983–88) and from 1988 he was Senior Scientist and Deputy Director at the IMP in Vienna, Austria. Since 2008 he was Vice Director (2008–11) and Director of the Cancer Cell Biology Program at the CNIO, Madrid. His work focuses on understanding gene functions in mammalian development and disease/cancer, employing genetic mouse models for human diseases.

Stem cells are essential for the maintenance and repair of most adult renewing tissues and organs including the gut, the blood or the skin. Historically stem cells have mostly been studied through transplantation experiments, in which the different cells of a tissue are individually separated and isolated based on expression of different cell surface proteins, physical characteristics or transcripts. These populations are transplanted into recipient mice to assess their ability to engraft, self-renew, expand and differentiate, giving rise to one or more lineages of their tissue of origin. While these experiments are very important to understand the potential of stem cells under regenerative conditions, it may not necessarily reflect the function of these cells in physiological conditions in their natural environment.

In a series of topical reviews, the authors highlight the latest advances in stem cell differentiation and disease ranging from studying at the single cell level how tissue homeostasis is achieved, describing how cells balance symmetric and asymmetric cell division and how this balance is perturbed during regenerative conditions, to progress in inflammation and cancer. Recent studies have shown that the fate of adult stem cells can be modified during regeneration and by cell signaling, and developmental pathways associated with cellular plasticity and reprogramming were also identified.

Fate mapping and tracking the stem cells

How lineage tracing approaches and clonal analyses are used to study the cellular hierarchy and cell proliferation dynamics during tissue maintenance and repair is discussed by Colom and Jones. The authors suggest that single equipotent progenitors rather than stem and progenitor hierarchy may regulate the homeostasis in different epithelia and possibly even during tumorigenesis. Single cell studies and clonal analysis using different CRE strains are essential to validate this simple model of tissue homeostasis. The impact of the microenvironment in regulating the spatial heterogeneity in cell fate decision, tissue repair and tumor initiation capacities is being recognized in tissues previously thought to be composed by equipotent progenitors (Sanchez-Danes A. *et al*. *Nature* 2016: 536; 298–303).

In a provocative review on 'Output without input' Höfer and Rodewald explain how recent fate mapping experiments challenge the current model and hierarchy of hematopoietic stem cells (HSCs) *in vivo*. The authors suggest that the blood lineages are maintained by a low cellular output from large numbers of HSCs during adult hematopoiesis and propose that cell proliferation increases and self-renewal decreases as cells progress from HSC to more committed progenitors. These novel methods to study HSCs within

their natural environment will be essential to study how patho-physiological conditions such as viral infection, chemotherapy or ageing affect the structure of the hematopoietic hierarchy and lineage differentiation.

Lineage tracing experiments in animals have been performed at different time points affecting the global view of the clonal dynamics of stem cells over time. Novel approaches allowing the direct visualization of stem cells and progenitors *in vivo* in living animals have been developed to see these cells in action in real time. Park, Greco and Crockburn review how intra-vital microscopy advances the field of stem cell biology by providing definitive demonstration for concepts previously suggested by analysis of fixed samples, but also by providing novel and unexpected insights of tissue development, homeostasis and cancer development, such as positional cues in stem cell fate regulation and cellular reprogramming during tumor initiation.

Clonal analysis provides important information on the functional heterogeneity within stem and progenitor cells that cannot be inferred from population analysis. Likewise, gene expression can now be analyzed at the single cell level allowing to dissect the molecular heterogeneity within different tissues and organs. Moignard and Göttgens review new approaches in single cell profiling at the whole genome level to uncover novel cell populations, lineage relationship within tissues and genes regulating lineage segregation and differentiation. It was assumed that once a given tissue completes development and reaches its final size, the different cells within the tissue are maintained by cells with a restricted lineage differentiation potential. However, during tissue regeneration, cells may de- or trans-differentiate and acquire a broader fate potential than usually present during homeostasis in a process called cell plasticity. Tata and Rajagopal review through an interesting historical perspective, how the concept of stem cell plasticity emerged, what are the patho-physiological or experimental context during which cell plasticity can be observed and what are the molecular mechanisms regulating cell plasticity in mammals. Furthermore, Moya and Halder highlight how Hippo signaling has recently emerged as an essential signaling pathway required for cell plasticity and tissue regeneration. The authors discuss how gain and loss of function experiments of components of the Hippo signaling pathway such as YAP/TAZ, which mediate transcriptional regulation downstream of the Hippo pathway, in different organs including heart, liver and pancreas affect embryonic development, homeostasis, regeneration and tumorigenesis.

Stem cells in action

To ensure tissue equilibrium, stem cells have to give rise to one stem and one committed cell, in a process called asymmetric cell renewal. Asymmetric cell renewal at the population level is achieved at the cellular level by the balance between asymmetric/symmetric cell renewal as well as symmetric cell divisions. Chen, Fingerhut and Yamashita discuss how extracellular cues from the stem cell niche along with intracellular mechanisms such as polarity proteins, centrosome position/age and cilia outgrowth govern asymmetric division and regulate the balance between self-renewal and differentiation thereby controlling tissue homeostasis and disease.

This balance is essential during development and tissue maintenance, where transcription factors, epigenetic modifiers and chromatin remodeling complexes control cell identity and differentiation. Mas and Di Croce focus their review on genes controlling stem cell identity, such as the Polycomb proteins, which control histone modifications and the epigenetic landscape. The authors elaborate how three dimensional organization and topology within the nucleus contribute to form a genome architecture required for stem cell renewal and differentiation.

The accurate dynamics of stem cell proliferation and differentiation ensures that the correct cell numbers are generated during homeostasis and tissue repair. Rulands and Simons discuss the power of bio-statistical approaches and quantitative analysis of lineage tracing experiments to understand the proliferation dynamics and lineage hierarchy of stem cells and progenitors during development and adult homeostasis in different tissues and organs. This analysis reveals that stem cell division and the balance between cell renewal and differentiation can be stochastically regulated. The authors also discuss how these homeostatic mechanisms are corrupted during tumor initiation and progression.

Organoids — the new tool kit

Although animal models have been instrumental to better understand the cellular and molecular basis of development, homeostasis and diseases, these models do not always perfectly mimic the situation in humans. In addition, many human tissues and organs cannot be studied *in vitro* in conventional culture conditions. For these reasons, new cellular models using human cells are warranted. Scheiger and Jensen describe how 3D organoids now enable to culture and expand various stem cells from different tissues and organs, and differentiate them into structures that mimic their tissue of origin in so-called mini-organs. The authors further explain how these organoids can be used to understand the mechanisms regulating human development, to establish models for different human diseases, and screen for new molecules that will be useful in different clinical settings.

In a timely and topical review by Muffat, Li and Jaenisch, the authors describe the power of using patient-derived induced pluripotent stem cells (iPSCs) to model human CNS disease, such as Alzheimer's or Parkinson disease

employing 3D organoids combined with the almost unlimited power of the CRISPR/Cas9 system. The expectation is that these novel methods will allow studying human neurological diseases in the relevant molecular, cellular and anatomical context, which holds great promise for future therapeutic applications.

Cancer, metastasis, inflammation and the RNA world

Epithelial to mesenchymal transition (EMT) is intensely studied and is an important process of cell remodeling during development and organogenesis. In EMT, epithelial cells lose their polarized organization and acquire migratory and invasive properties, which are hallmarks of migrating metastatic cells. The article by Diepenbruck and Christofori points out the limitations of this textbook knowledge, since recent experiments question the role of EMT in metastasis. Remarkably, the reverse process called mesenchymal to epithelial transition (MET), seems to favor metastatic outgrowth, although more thorough fate-mapping experiments are needed to obtain a better understanding of this important event.

It is commonly accepted that normal tissue regeneration and repair are dysregulated in chronic diseases including aging and cancer, which involve the immune system in form of acute or chronic inflammation. In particular in colon and pancreatic cancers, an inflammatory tumor microenvironment constitutes a cancer hallmark. The signaling cascades within the tumor, but also in the surrounding stromal cells, are about to be unraveled as reported in the article by Pesic and Greten.

Finally, the article by Pasut, Matsumoto, Clohessy and Pandolfi alerts us of the ever increasing complexity of non-coding genes/RNAs, which appear to be involved in almost any biological process in form of a large variety of micro-, circular and long non-coding RNAs. The article describes the new discoveries in RNA research in particular in the field of development and cancer, and leaves us with the optimistic view that novel insights into RNA biology will pave the road for RNA-based drugs/medicines in the years to come.

Perspectives

The important progress made in stem cell biology provides the basis for future studies that will elucidate the role of stem cells and progenitors in regulating tissue maintenance, regeneration, differentiation and how these processes are altered in disease. Single cell analysis and next generation sequencing will continue to yield new insights into the cellular diversity, the genetic and epigenetic processes that control mechanisms regulating cell fate decisions. Differentiation therapies for proliferative diseases should also be kept in mind as a promising tool for future clinical applications. Importantly, we will see in the near future that whole-organism physiology and the crosstalk between organs will become increasingly important to better understand the mechanisms underlying chronic diseases, such as inflammation, the metabolic syndrome, diabetes, chronic heart and neurological diseases, but also in cancer and cancer-associated-cachexia (Petruzzelli M. and Wagner EF. Genes Dev. 2016: 30; 489–501). These approaches aiming to understand the whole system and not only the parts together with new targets derived from such studies will become center-stage for the next generation medicines in the years to come.