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La série de cours donnés les 8, 15, 18 et 22 janvier 2008 a porté sur les sujets suivants :

1. Stem Cells : Biology, Ethics and potential for Medicine ;
2. The Biology and Genetics of Skin and Hair ;
3. Cell adhesion, Migration and Cancer ;
4. Stem Cells of the Skin and their Lineages.

1. Stem Cells : Biology, Ethics and potential for Medicine

The remarkable ability to generate an embryo from a single fertilized oocyte, to periodically replace dying cells within tissues and to repair tissues damaged during injury, is a direct consequence of stem cells, nature's gift to multicellular organisms. The gold standard of stem cells is the fertilized egg, which produces an organism replete with ~220 specialized cell types, including reproductive germ stem cells. As the embryo first develops, an outer protective shell of support cells, referred to as the trophectoderm, encases an undifferentiated mass (the inner cell mass) of pluripotent embryonic stem (ES) cells that will make the animal. As tissues and organs develop, stem cells become more restricted in their options(Fuchs et al. 2004; Fuchs 2007).

Although cell type specification is largely complete at or shortly after birth, organs must possess a mechanism to replenish those cells within the tissue that die or become damaged with age. This process of cell replacement by natural wear and tear is referred to as homeostasis, and is fueled by adult stem cells which typically reside within a tissue. Some tissues, like the skin epidermis or intestinal epithelium, undergo constant turnover and rejeuvenation involving the entire tissue. For other tissues/organs, e.g. the brain, it has only been recently that scientists have appreciated the existence of stem cells that have the ability to replenish specialized neurons, glial cells and oligodendrocytes over time, even if this capacity is much reduced in comparison to the hematopoietic system or epithelial tissues. Increasing evidence is pointing to the view that most tissues of the body have adult stem cells.

Like ES cells, adult stem cells undergo self-renewal, the ability to divide to generate self, and the ability to generate cells that will differentiate to produce tissues. Adult stem cells, however, typically give rise to only a few different types of tissues, a feature often referred to as multipotent. Some stem cells, e.g. germ stem cells, are thought to give rise to only one lineage, in this case, either oocyte (female germ stem cells) or sperm (male germ stem cells). Given the fountain of youth ability of adult stem cells to generate tissues during normal homeostasis and wound-repair, these stem cells are typically set aside in protected reservoirs within the developing tissue. They are often used sparingly, and hence undergo fewer divisions than their activated progeny. The protective niches are composed not only of stem cells but also a complex “microenvironment” of neighboring differentiated cell types which secrete and organize a diverse range of extracellular matrix and other factors that allow stem cells to manifest their unique intrinsic properties(Fuchs et al. 2004; Moore and Lemischka 2006; Morrison and Kimble 2006).

Harnessing adult stem cells for regenerative medicine has long been a major focus of scientists and clinicians alike. Examples of the successful use of stem cells for regenerative medicine include bone marrow transplants to replace cells of the hematopoietic system and cultured epidermal sheets for the replacement of epidermis lost in badly burned skin (Weissman 2000; De Luca et al. 2006). ES cells have received more attention because of their broader potential and hence greater promise for generating cell types to treat injuries and degenerative conditions for which we presently have no cures. With the promise are also ethical considerations dealing with the use of fertilized eggs for research necessary to harness this potential. Scientists have countered with technology referred to as nuclear transfer, often mistakenly referred to as human cloning. This technology involves making a hybrid somatic cell from an unfertilized oocyte whose nucleus was removed and replaced by an adult

somatic cell(Hochedlinger and Jaenisch 2006). In collaboration with the laboratory of Peter Mombaerts at the Rockefeller University, my laboratory has used this technology to demonstrate that ES cells and in fact healthy viable mice could be generated from hybrid diploid totipotent cells, each composed of an unfertilized enucleated mouse oocyte and an adult hair follicle stem cell, normally able to differentiate into only epidermis, hair follicles and sebaceous glands(Blanpain and Fuchs 2006; Li et al. 2007). Although nuclear transfer technology has not yet been successful for generation of human ES cells, scientists recently succeeded in generating primate ES cells through nuclear transfer (Byrne et al. 2007).

Can adult skin cells be utilized to generate ES cells directly, without the use of an unfertilized oocyte? Breakthroughs over the past year have led scientists to predict that this may be possible in the future. In a pioneering study published in summer, 2007, Yamanaka and coworkers reported the generation of germline competent "induced pluripotent stem cells" (iPS cells) generated by retroviral infection of mouse skin fibroblasts to force the expression of four transcription factors normally expressed by ES cells but not by adult somatic cells(Meissner et al. 2007; Okita et al. 2007). Unfortunately, one of the transcription factors was a potent cell cycle stimulator and the mice generated developed tumors with time. Since this time, however, researchers have now succeeded in eliminating this gene from the mix, and now only three transcription factors appear to be sufficient (Nakagawa et al. 2008; Park et al. 2008). Moreover, in animal mouse models of human disease, iPS cells have already shown promise for treatments (Hanna et al. 2007), and in the past several months, two groups have independently succeeded in generating human iPS cells from adult skin cells (Takahashi et al. 2007; Yu et al. 2007).

This explosion of research bodes well for the future of human regenerative medicine. The challenge now will be how to avoid the genetic manipulation (in some cases, >50 integrated retroviral DNAs) that occurs in generating iPS cells and/or overcoming the present hurdles in generating human ES cells by nuclear transfer. While nuclear transfer is preferable in using epigenetic reprogramming rather than genetic manipulation, it still uses unfertilized oocytes. That said, the excitement and promise of stem cells for regenerative medicine continues to grow and 2007 has been a very successful year in overcoming technological barriers that less than a decade ago were thought to be insurmountable.

2. The Biology and Genetics of Skin and Hair

The skin epidermis and its appendages provide a protective barrier that is impermeable to harmful microbes and also prevents dehydration. To perform their functions while being confronted with the physico-chemical traumas of the environment, these tissues undergo continual rejuvenation through homeostasis and in addition, they must be primed to undergo wound-repair in response to injury. The skin's fountain of youth for maintaining tissue homeostasis, regenerating hair and repairing the epidermis following injury is its stem cells, which reside in the adult hair follicle, sebaceous gland and epidermis. Stem cells have the remarkable capacity to both self-perpetuate and also give rise to the differentiating cells that constitute one or more tissues. In recent years, researchers have begun to uncover the properties of skin stem cells, and unravel the mysteries underlying their remarkable capacity to perform these feats.

The adult skin epithelium is composed of molecular building blocks, consisting of a pilosebaceous unit (HF and sebaceous gland) and its surrounding interfollicularepidermis (IFE)(Blanpain and Fuchs 2006). Both the IFE and the sebaceous gland contain their own progenitor cells for normal homeostasis in the absence of injury(Levy et al. 2005; Horsley et al. 2006; Levy et al. 2007). HFs contain a niche of relatively quiescent follicle stem cells that are normally activated at the start of each new hair cycle. Upon wounding, these cells are able to repair the epidermis and sebaceous glands. Like many other adult stem cells of the body, skin epithelial stem cells were predicted to be relatively infrequently utilized, and hence slow-cycling (Taylor et al. 2000; Oshima et al. 2001). Like

other stratified squamous epithelia and many glandular epithelia, the skin epithelial cells with proliferative activity were known to express keratins 5 and 14 (Fuchs and Green 1980; Vassar et al. 1989). On the basis of these two characteristics, we devised a pulse-chase strategy with a fluorescent histone to identify and fluorescently mark the slow-cycling K5/K14-positive cells of mice(Tumbar et al. 2004). Located in a region of the hair follicle known as the bulge, special cells within this niche could be activated to proliferate and divide with each new hair cycle and could be mobilized to repair wounds to the epidermis. Using fluorescence activated cell sorting, cell culture, and skin engraftments with clonally derived progeny of single bulge cells, we showed that these cells are in fact stem cells, and they have multipotent capacity(Blanpain et al. 2004; Morris et al. 2004; Tumbar et al. 2004; Ito et al. 2005).

We've used transcriptional profiling and genetic analyses to understand how these stem cells maintain quiescence and become activated upon initiation of a new hair cycle. We've revealed roles for the Wnt signaling pathway in stem cell activation, self renewal, hair shaft production and tumorigenesis (Zhou et al. 1995; Gat et al. 1998; Chan et al. 1999; DasGupta and Fuchs 1999; Merrill et al. 2001; McLean et al. 2004; Lowry et al. 2005; Nguyen et al. 2006). We've revealed roles for the BMP pathway in controlling stem cell quiescence(Kobielak et al. 2003; Kobielak et al. 2007; Horsley et al. 2008). Collectively, the studies from my laboratory and others(Huelsken and Birchmeier 2001; Van Mater et al. 2003; Andl et al. 2004; Lo Celso et al. 2004; Ito et al. 2007) suggest a working model for stem cell quiescence, self-renewal and activation in the hair follicle during normal homeostasis and wound repair.

3. Cell adhesion, Migration and Cancer

The skin epidermis is an excellent example for exploring homeostasis and injury repair in a stratified epithelium. The epidermis maintains a single inner (basal) layer of proliferative cells that adhere to an underlying basement membrane rich in extracellular matrix (ECM) and growth factors (Fuchs 2007). Basal cells express a number of characteristic markers including keratins and transcription factors. Periodically, these cells withdraw from the cell cycle, commit to differentiate terminally, move outward and are eventually shed from the skin surface. This architecture allows the epidermis to generate a self-perpetuating barrier that keeps harmful microbes out and essential body fluids in.

Upon commitment to terminally differentiate, an epidermal keratinocyte progresses through three distinct differentiation stages: spinous, granular and stratum corneum. Major changes in transcription, morphology and function occur at the basal/spinous layer transition and again at the granular/stratum corneum transition, such that differentiated cells reaching the skin surface are enucleated, cellular skeletons that are packed with cables of keratin filaments encased by an indestructible envelope of proteins. An additional final step in the differentiation process is the extrusion of a lipid bilayer that seals and protects the body surface from dehydration and harmful microbes. The process is in a continual homeostasis, so that surface cells are continually sloughed and replaced by inner cells differentiating and moving outward. In human epidermis, the self-renewing capacity of epidermal stem cells is enormous, and within 4 weeks, a basal cell has terminally differentiated and exited at the skin surface. In mice, the epidermis becomes thinner and proliferation slows substantially as the hair coat develops.

To coordinate epidermal homeostasis and wound-repair and to maintain a single layer of dividing cells and multiple layers of differentiating cells, the epidermis displays an elaborate cytoskeletal architecture. Ten nanometer wide intermediate filaments composed of keratin proteins are the major cytoskeletal component of the epidermis and its appendages. Dividing cells express keratins 5 and 14, while differentiating epidermal cells express keratins 1 and 10 (Fuchs and Green 1980). The basic subunit structure of the keratin filament is an obligatory heterodimer of type I and type II keratins(Fuchs et al. 1981; Hanukoglu and Fuchs 1982; Hanukoglu and Fuchs 1983; Coulombe and

Fuchs 1990)). The function of these keratins is to impart mechanical integrity to the epidermis, without which the cells become fragile and prone to rupturing upon physical stress (Albers and Fuchs 1987; Albers and Fuchs 1989; Coulombe et al. 1990; Vassar et al. 1991; Letai et al. 1992)). First discovered in mice and then in humans, the blistering skin disease epidermolysis bullosa simplex (EBS) is a genetic disorder of keratins 14 and 5 (Bonifas et al. 1991; Coulombe et al. 1991; Lane et al. 1992; Fuchs and Weber 1994), and the blistering disorder epidermolytic hyperkeratosis is a genetic disorder of keratins 1 and 10(Cheng et al. 1992; Chipev et al. 1992; Rothnagel et al. 1992). There are now more than 20 different IF disorders in humans, and many of these set the paradigm first discovered for EBS (Fuchs and Cleveland 1998; Omary et al. 2004).

To form a cytoskeleton, keratin filaments associate with α6β4 integrin-rich hemidesmosomes at the base of the basal epidermal cell, and desmosomal-cadherin-rich desmosomes to make cell-cell junctions. When these IF-adhesive connections are defective, mechanical fragility and degenerative disorders also occur. By contrast, the actin cytoskeleton associates with α3β1 integrin-rich focal adhesions and to E-cadherin rich adherens junctions (Perez-Moreno et al. 2006). We've used gene targeting to conditionally mutate the genes encoding E-cadherin, α-catenin and p120-catenin from the skin epidermis(Vasioukhin et al. 2000; Vasioukhin et al. 2001; Tinkle et al. 2004; Kobielak and Fuchs 2006; Perez-Moreno et al. 2006)). Intriguingly, mutations in all of these genes render the skin epithelium prone to squamous cell carcinomas and/or proinflammatory responses. We've shown that α-catenin is particularly important not only for coordinating adhesion-actin dynamics but also proliferation, invasion, and inflammation (Vaezi et al. 2002; Jamora et al. 2003; Kobielak and Fuchs 2006).

Interestingly, it is also required for proper spindle orientation in the epidermis, a process which requires actin-microtubule polarization. During embryonic development as the epidermis transits from a single layer to a stratified layered epithelium, spindle orientation changes to become asymmetric relative to the basement membrane. Mechanistically, the process appears to involve many of the proteins used by fly neuroblasts in asymmetric divisions that generate neurons (Lechler and Fuchs 2005).

In addition to requiring α-catenin, the process of asymmetric divisions in the epidermis also relies upon β1 integrin (Lechler and Fuchs 2005). We've targeted β1 and its downstream tyrosine kinase effector, focal adhesion kinase (FAK) for ablation in the skin (Raghavan et al. 2000; Raghavan et al. 2003; Schober et al. 2007). Without β1 integrin, basement membrane assembly is defective and hair follicles cannot invaginate. Epidermal cells also fail to activate FAK and focal adhesion turnover, necessary for efficient cell migration, is impaired(Schober et al. 2007). Without FAK, the skin epidermis becomes more resistant to tumorigenesis(McLean et al. 2004; Schober et al. 2007) . Interestingly, TGFβ signaling may also be linked to focal adhesions, as without TGFβ signaling, the skin is more susceptible to tumorigenesis and FAK is upregulated(Guasch et al. 2007).

In summary, in the nearly three decades of skin biology research conducted by my laboratory, an understanding is beginning to emerge of how multipotent stem cells receive external signals to change their programs of transcription and gene expression, remodel their cytoskeletal-adhesive contacts and generate tissues. In the case of skin, one of the remarkable features of these multipotent stem cells is their ability to generate the epidermis, hair follicle and sebaceous gland, three fascinating and strikingly distinct tissue structures. With the future promise of the skin as a possible source for generating embryonic stem cells, the skin may well not only prove to be our largest organ and our largest immune system of the body, but also our most important source of material for the future of regenerative medicine.

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