Fat or Fiction: Origins Matter

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Cell-lineage tracing has revealed a complex heterogeneity present in postnatal tissue and adult progenitors. Chau et al. (2014) and Long et al. (2014) provide further evidence for this among adipocytes, and their findings underscore the importance of cellular ontogeny not just for development but also for potential treatment of disease.

Origins matter. While this axiom may be debatable on a global scale given constantly changing geopolitical landscapes and regression of ethnocentric thought, on the level of an individual organism, the importance of origin cannot be ignored. Experiments in fate mapping of embryonic tissue have been performed for nearly a century, but in more recent years, developments in transgenic techniques and fluorescent peptide tracers have allowed for more granularity with single-cell resolution. Studies by Chau et al. (2014) and Long et al. (2014) have employed these advances, and their findings help to highlight the importance of cellular ontogeny, not only from a developmental perspective but also for tissue homeostasis, development of disease, and tissue repair/regeneration.

Given the rise in obesity and associated metabolic disorders, considerable interest in the developmental origins of adipose tissue has developed. Of particular significance has been the revelation of heterogeneity among fat, which may reflect diversity in embryological origin (Billon and Dani, 2012). In a recent report by Chau et al. (2014), major ontogenetic differences in visceral and subcutaneous white adipose tissue were described, and cell-lineage analysis based on Wilms' tumor gene, Wt1, expression revealed significant lateral plate mesoderm contribution to development of visceral adipocytes. This contrasts with the known contribution to subcutaneous and brown adipocytes from paraxial mesoderm and neural crest. Importantly, however, Chau et al. (2014) also noted intradepot heterogeneity among visceral adipocyte precursors, as Wt1 expression among preadipocytes was not uniform. While preliminary studies found this to manifest in variable numbers of lipid droplets per cell, whether this translates to differences in metabolic properties and what implications this may have on obesity and obesity-associated diseases have yet to be fully elucidated.

Further level of detail into the cellular heterogeneity of fat has now been provided by Long et al. (2014), who employed a transcriptional profiling approach and in vivo fate mapping to probe distinct subsets of thermogenic adipocytes. While two types of these specialized fat cells are known to exist—classical brown fat and beige fat found interspersed in various white fat depots—studies have shown distinct cellular ontogeny, which is likely reflected in different behavior and function. Brown fat precursors arising from paraxial mesoderm express *Myf5*/*Pax7* indicative of a skeletal muscle lineage. In contrast, Long et al. (2014) surprisingly noted beige fat to be associated with a constellation of markers classically associated with smooth muscle. Lineage tracing using *Myh11*, a selective marker for smooth muscle cells, demonstrated a significant proportion of UCP-1 positive cells in inguinal fat to derive from mature *Myh11*-expressing cells. These findings provide an interesting context from which to interpret crosstalk between perivascular adipocytes and vascular smooth muscle. They also underscore the significance of cellular origin, as these ontogenetic differences likely contribute to observations of preferential browning and baseline/inducible thermogenic behavior in various fat depots (Seale et al., 2011).

Heterogeneity and an appreciation for cellular ontogeny, however, extend far beyond that of adipose tissue, and recapitulation of this theme can be found throughout multiple other systems. Skin is constantly turned over, and the epidermis is completely replaced every 28 days. Whether newly generated skin is thin and hair bearing for the face and scalp or thick and hairless for the palm and sole is dependent on a complex interplay of disparate progenitor cells and their positional/ontogenetic memory. In recent years, new populations of stem cells have been identified residing in the hair follicle or interfollicular epidermis, and studies have revealed a complex temporospatial interplay during states of health and injury highlighting the diversity of cells at work (Ghazizadeh and Taichman, 2001). Reports have shown some of this may be regulated by maintenance of *HOX* profiles, which in turn activate specific transcriptional programs dictating epidermal differentiation patterns (Rinn et al., 2008). In addition, fibroblast precursors derived from mesenchymal stem cells have been found to faithfully express position-specific *HOX* genes, which reflect the embryonic segment from which they are derived. Unpublished work from our own laboratory has also identified heterogeneity among fibroblasts and has shown distinct populations to directly contribute to development of scars.

From the perspective of bone, distinct embryologic derivation of osteoblasts has also been found to impart variable bone-forming potential and regenerative capacity. Lineage-tracing studies have demonstrated a neural crest origin for frontal bone and paraxial mesoderm contribution to parietal bone. Importantly, this is reflected in origin-specific Wnt and FGF-signaling differences, resulting in superior intrinsic osteogenic potential and tissue regeneration capacity among

neural crest-derived frontal osteoblasts (Quarto et al., 2010.) Furthermore, heterogeneity among osteoprogenitors may also have direct implications on healing, as embryonic origin of skeletal stem cells has been shown to determine progenitor cell fate during bone repair (Leucht et al., 2008). Lastly, as Chau et al. (2014) noted, depot-specific differences in osteoblast forming capacity was found among the stromal vascular fraction from various fat pads. This same observation has been made from our own laboratory, and sifting through heterogeneity of adipose-derived stromal cells will be critical for future efforts in bone tissue engineering.

Finally, understanding cellular ontogeny may have direct implications on the treatment of disease. For example, integrated genomic studies have revealed medulloblastoma to be comprised of four distinct molecular subsets with variable clinical behavior. One of these subtypes, WNT, has been shown to arise from cells of the dorsal brainstem outside the cerebellum, which contrasts with other subtypes arising from granule neuron precursor cells (Gibson et al., 2010). This distinction has become important in that proliferation of granule neuron precursors may be regulated by FGF and treatment of medulloblastoma-bearing mice with this growth factor markedly inhibits tumor activity (Emmenegger et al., 2013). Thus, future molecular targeting of tumors may depend on an appreciation of where these cells arise.

Origins matter, and not just from a developmental perspective. Recognition of cellular ontogeny provides a necessary context to begin to address issues with homeostasis, disease, and tissue repair. In light of findings by Chau et al. (2014) and Long et al. (2014), an appreciation of origin may facilitate development of more targeted therapeutics aimed at specific adipocytes for treatment of metabolic syndrome. And given the heterogeneic complexity of postnatal tissue and resident adult progenitor cells, comprehension of ontogenetic differences may also yield new strategies for tumors such as liposarcoma, healing of soft tissue and bone, and treatment of a variety of other disorders.

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