

RETROSPECTIVE

The Adipose-derived Stem Cell: Looking Back and Looking Ahead

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In 2002, researchers at UCLA published a manuscript in *Molecular Biology of the Cell* describing a novel adult stem cell population isolated from adipose tissue—the adipose-derived stem cell (ASC). Since that time, the ASC has gone on to be one of the most popular adult stem cell populations currently being used in the stem cell field. With multilineage mesodermal potential and possible ectodermal and endodermal potentials also, the ASC could conceivably be an alternate to pluripotent ES cells in both the lab and in the clinic. In this retrospective article, a historical perspective on the ASC is given together with exciting new applications for the stem cell being considered today.

Over the last 10 years, giant strides have been made worldwide in the adult stem cell field. It seemed every month another groundbreaking article was being published describing a unique adult stem cell population from a tissue we never could have imagined. Skin, liver, digestive epithelium, dental pulp, hair follicles—even amniotic fluid appeared to be a stem cell source that could be manipulated in the laboratory in wonderful ways. However, at the start of the decade, the number of adult stem cells being studied seemed to be limited to a few, but in 2002, our team at UCLA had the privilege of being able to add to the adult stem cell roster with the publication of a manuscript in *Molecular Biology of the Cell* (Zuk *et al.*, 2002) that characterized a stem cell population from human adipose tissue. Since then it seems that the adult stem cell field has “taken off” into new and exciting territories.

ADULT STEM CELLS AND THE ASC: A BRIEF HISTORY

At its heart there are essentially only two categories of stem cells: the embryonic stem cell (ES cell) and the postnatal stem cell (i.e., adult stem cell). The ES cell, as its name implies, is derived from the embryo—more specifically, from the blastocyst’s inner cell mass. The adult stem cell, in contrast, is derived from postnatal tissues and can include fetally derived stem cells and umbilical cord blood stem cells.

Despite the impression given to most people by the mainstream media, the adult stem cell field isn’t a recent development. In fact, the origins of the field can be traced back to the laboratory of Ernest McCulloch and James Till at the Ontario Cancer Institute in Toronto. In two groundbreaking articles published in 1963, McCulloch and Till, with Andy Becker and Lou Siminovitch, reported on the presence of

self-renewing cells within the bone marrow of mice and postulated that these cells were regenerative stem cells (Becker *et al.*, 1963; Zhang *et al.*, 1999). Of course, we now know these cells to be hematopoietic stem cells (HSCs), the first described adult stem cell, although one could argue for the muscle-derived satellite cell described in 1961 to take this title (Mauro, 1961; Moss and Leblond, 1971). From the work of McCulloch and Till, the adult stem cell field gathered momentum in the late sixties and early seventies as patients suffering from SCID (severe combined immunodeficiency) were treated using bone marrow transplants or HSC concentrates (Dicke and van Bekkum, 1973; Lin *et al.*, 2000). In 1978, HSCs were identified in umbilical cord blood and a new population of adult stem cells was born: the umbilical cord blood stem cell (Emerson *et al.*, 1985; Broxmeyer *et al.*, 1990). The late 1960s also saw the introduction of the bone marrow mesenchymal stem cell (MSC; Friedenstein *et al.*, 1968). Finally, in 1992, the adult stem cell list grew again with the work of Reynolds and Weiss (1992), who described neural stem cells isolated from murine striatal tissue.

Until the year 2000, adult stem cell articles seemed to be limited to the HSC, the MSC, the NSC (neural stem cell) and the muscle satellite cell. However, 2001 saw the addition of another adult stem cell to the roster: the adipose-derived stem cell (ASC). In the journal *Tissue Engineering* our team first used the term processed lipoaspirate (PLA) cells, owing to their isolation from human lipoaspirates, and proposed that the ASC was a multilineage stem cell population that could be isolated from the stromo-vascular fraction of adipose tissue (Zuk *et al.*, 2001). Why adipose tissue would contain a stem cell population is not that far-fetched. The conversion of adipose tissue to calcified bone has been observed in several diseases including lupus, subcutaneous fat necrosis (Shackelford *et al.*, 1975) and Paget’s disease (Clarke and Williams, 1975). This conversion should not be possible by the resident, unipotent preadipocyte precursor population. Also, adipose tissue is derived from the embryologic

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mesenchyme and possesses a well-described stroma that like bone marrow could feasibly contain a mesenchymal stem cell population. The initial results published in *Tissue Engineering* seemed to support this theory.

To confirm this theory, our team undertook a more extensive molecular and biochemical analysis of the ASC (i.e., the PLA cell) in our 2002 MBoC article (Zuk *et al.*, 2002). This article not only confirmed our earlier work that the ASC is capable of differentiating into multiple mesodermal cell types—adipogenic, chondrogenic, osteogenic, and myogenic (Zuk *et al.*, 2001), but utilized additional approaches such as the expression of multiple lineage-specific genes and functional biochemical assays to confirm this property. Combining these approaches, the data of our MBoC article appeared to fulfill one important requirement of a stem cell: differentiation capacity. However, the MBoC article also fulfilled another important requirement specific to adult stem cells, that of *clonogenicity*. One of the most obvious hurdles for adult stem cell identification is the heterogeneity of their origin tissue. Because of this, the observed multilineage differentiation by ASCs may simply be due to the presence of multiple precursor populations, each completing their development. One way to circumvent this would be the isolation of a stem cell, combined with proof of its multipo-

tency. Therefore, the 2002 MBoC article also contained data confirming multilineage differentiation of *single ASC clones*.

Having demonstrated differentiation capacity and clonogenicity, we felt confident that the ASC was, in fact, a new adult stem cell population and, since 2002, many groups have confirmed our proposal in both human and animal ASC populations. The ability of both human and animal ASCs to undergo mesodermal differentiation at the in vivo level has also been presented using a wide variety of animal model systems, but what has become more exciting is the potential of ASCs beyond the mesodermal lineage. Our original MBoC article suggested that ASCs might possess the ability to differentiate to neuronal-like cells of the ectodermal lineage. Confirmatory studies examining this capacity quickly followed (Safford *et al.*, 2002; Ashjian, 2003). Today, the ability of ASCs to form cells consistent with neurons (Kang *et al.*, 2004), oligodendrocytes (Safford *et al.*, 2004), functional Schwann cells (Kingham *et al.*, 2007; Xu *et al.*, 2008), and cells of the epidermal lineage (Trottier *et al.*, 2008) have added credence to the theory that ASCs may be pluripotent rather than multipotent. Not surprisingly, studies describing the endodermal differentiation of ASCs have also appeared, with ASCs being induced to form hepatocytes and pancreatic islets (Seo *et al.*, 2005; Timper *et al.*, 2006). The

Table 1. Current application of ASCs: a summary

	References
ASC research activity	
Adipose tissue	Mauney <i>et al.</i> , 2007
Bone tissue	Cowan <i>et al.</i> , 2004; Dudas <i>et al.</i> , 2006; Yoon <i>et al.</i> , 2007
Cartilage	Dragoo <i>et al.</i> , 2003; Guilak <i>et al.</i> , 2004
Skeletal muscle	Bacou <i>et al.</i> , 2004; Goudenege <i>et al.</i> , 2009
Smooth muscle	Rodriguez <i>et al.</i> , 2006
Neural	Ashjian, 2003; Safford <i>et al.</i> , 2004; Erba <i>et al.</i> , 2009; Nakada <i>et al.</i> , 2009
Vocal fold/laryngeal tissue	Kumai <i>et al.</i> , 2009; Long <i>et al.</i> , 2009
Bladder/urethra	Jack <i>et al.</i> , 2005
Cardiovascular tissue/vascular tissue	Miranville <i>et al.</i> , 2004; Heydarkhan-Hagvall <i>et al.</i> , 2008; Froehlich <i>et al.</i> , 2009; Okura <i>et al.</i> , 2009c
Hematopoietic	Cousin, 2003; Puissant <i>et al.</i> , 2005
Pancreatic tissue/islet development	Timper <i>et al.</i> , 2006; Okura <i>et al.</i> , 2009a; Kajiyama <i>et al.</i> , 2010
Hepatic tissue	Seo <i>et al.</i> , 2005; Banas <i>et al.</i> , 2007; Okura <i>et al.</i> , 2009b
Epithelial/skin tissue	Brzoska <i>et al.</i> , 2005; Jeong, 2009
Kidney tubule epithelial cell	Li <i>et al.</i> , 2009
ASCs in disease and injury	
Intervertebral disc repair	Hsu <i>et al.</i> , 2008
Spinal cord injury	Ryu <i>et al.</i> , 2009
Peripheral nerve regeneration	di Summa <i>et al.</i> , 2009
Glioblastoma treatment	Josiah <i>et al.</i> , 2010
Huntington's	Lee <i>et al.</i> , 2009
Multiple sclerosis	Riordan <i>et al.</i> , 2009
Stroke	Kim <i>et al.</i> , 2007
Urinary incontinence	Lin <i>et al.</i> , 2010
Erectile dysfunction	Lin <i>et al.</i> , 2009a
Liver repair	Liang <i>et al.</i> , 2009
Diabetes	Lin <i>et al.</i> , 2009b
Colitis	Gonzalez-Rey <i>et al.</i> , 2009
Ischemia	Kondo <i>et al.</i> , 2009
Rheumatoid arthritis	Gonzalez-Rey <i>et al.</i> , 2010
Antiaging	Park <i>et al.</i> , 2008
Wound healing/skin regeneration	Trottier <i>et al.</i> , 2008
Cleft palate	Conejero <i>et al.</i> , 2006
Tendon repair	Uysal and Mizuno, 2009
ASC human trials	
Calvarial defect	Lendeckel <i>et al.</i> , 2004
Crohn's disease	Garcia-Olmo <i>et al.</i> , 2009; Taxonera <i>et al.</i> , 2009
Urinary incontinence	Yamamoto <i>et al.</i> , 2009
Graft vs. host disease	Fang <i>et al.</i> , 2007

theory that ASCs, like ES cells, may be pluripotent and capable of forming multiple cell types within all three germ layers was proposed.

THE WIDE, WIDE WORLD OF ASCs

The possibility that the ASC is pluripotent would obviously revolutionize the stem cell field. Why bother with the ethical and political difficulties of the ES cell when a plentiful source of similarly potent stem cells could be found in your fat? However, we have a long way to go with the ASC before such a statement should be seriously considered. Fortunately, researchers around the world consider the ASC exciting enough to make it the focus of their work. Today, a search of PubMed using the terms “adipose” and “stem cell” yields over 2000 entries, making the ASC one of the most popular adult stem cells currently being explored today.

Today, the proposed uses for ASCs in tissue repair/regeneration are quite impressive. Hot areas of research include ischemia revascularization, cardiovascular tissue regeneration, bone/cartilage repair, and urinary tract reconstruction (Table 1). With its mesodermal origin, the application of ASCs to bone and cartilage defects is obvious along with their use in tendon and intervertebral disk repair (Table 1). However, the use of ASCs is expanding to both the ectodermal and endodermal lineages. Work by di Summa *et al.* (2009) has suggested that rat ASCs may stimulate peripheral nerve repair, whereas Ryu *et al.* (2009) has observed functional recovery upon their transplantation into dogs with acute spinal cord damage. Liver injury repair may also be possible with transplantation of rat ASCs, decreasing key liver enzyme levels and increasing serum albumin (Liang *et al.*, 2009). Even diabetes may be a target for ASC therapy, with murine ASCs reducing hyperglycemia in diabetic mice (Kajiyama *et al.*, 2010). Most recently, researchers have begun to explore the potential uses of “reprogrammed” ASCs as iPS (induced pluripotent stem) cells and have suggested that the ASC may be easier to reprogram than the fibroblast (Sun *et al.*, 2009).

However, researchers are also beginning to “think outside the box.” The transplantation of human ASCs into a murine model of Huntington’s appears to slow progression of the disease, inducing the expression of neuroprotective genes by the host (Lee *et al.*, 2009). Human ASCs have recently been used to deliver myxoma virus to experimental gliomas in nude mice, making the ASC a possible vector for oncolytic viral treatment of brain tumors (Josiah *et al.*, 2009). Human ASCs engineered to convert 5-fluorocytosine to the antitumor drug 5-fluorouracil have also been used to inhibit prostatic tumor growth. Finally, the ability of ASCs to suppress specific aspects of the immune system (Puissant *et al.*, 2005) has created another exciting research avenue encompassing everything from organ antirejection to the amelioration of autoimmune diseases (Gonzalez *et al.*, 2009; Riordan *et al.*, 2009). Nothing seems to be out of the realm of possibility, with work by Park and colleagues investigating whether the secretory products from ASCs can act as antiwrinkle agents, promoting dermal thickness (Kim *et al.*, 2009). Even the popular topic of erectile dysfunction may be solved with the transplantation of ASCs (Lin *et al.*, 2009a)!

What might be more exciting is the application of ASC in our clinics. Although the excitement regarding the ES cell has picked up with the Obama administration’s approving an increase in the number of new ES lines and a limited human clinical trial, what many people don’t realize is that the ES cell has yet to treat any disease. This in contrast to the HSC, which has been utilized successfully in medicine for

the last four decades! On the basis of this, many researchers firmly believe that the adult stem cell might be more useful clinically useful than the ES cell. In support of this, there are emerging clinical applications of the ASC, which started in 2004 with the combination of ASCs and bone grafts to treat extensive craniofacial damage in a 7-year-old girl (Lendeckel *et al.*, 2004) to a recently completed stage II clinical trial for Crohn’s disease (Garcia-Olmo *et al.*, 2009). ASCs have also been applied in trials for urinary incontinence (Yamamoto *et al.*, 2009) and graft versus host disease (Fang *et al.*, 2007).

THE FUTURE OF ASCs

Looking back, the isolation of the ASC seemed to preface a decade that could easily be named the “decade of the adult stem cell,” with an impressive number of groundbreaking articles describing the isolation of adult stem cells not only from adipose tissue but from skin, liver, digestive epithelium, pancreas, and neural crest. Even tissues as unexpected as amniotic fluid, dental pulp, hair follicles, and eyelids have all been found to contain resident stem cell populations. However, the ASC does have one important advantage over these other sources—availability. There is no human tissue as expendable as adipose tissue, making it relatively easy to isolate adequate numbers of ASCs for possible human therapies. With this fact, together with the early clinical uses of ASCs that report no adverse effects, it would seem only a matter of time before more and more clinical applications of ASCs are reported. Although the ES cell with its proven self-renewal capacity and pluripotency would seem to be a more appropriate stem cell to use clinically, the recent work on ASCs would suggest that this adult stem cell may prove to be an equally powerful weapon in the treatment of human disease and injury. Only time will tell.

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