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Stem cell therapy in veterinary dermatology

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Background – Adult stem cells come from many sources and have the capacity to differentiate into many cell types, including those of the skin. The most commonly studied stem cells are those termed mesenchymal stem cells (MSCs), which are easily isolated from bone marrow and adipose tissue. Mesenchymal stem cells are known to produce a wide array of cytokines that modulate the regeneration process. The ease of collection, propagation and use of these MSCs in therapy of traumatic, ischaemic and immune-mediated skin conditions is emerging.

Approach and evidence – In traumatic and ischaemic skin damage, MSCs are used in tissue-engineered skin and by direct injection into damaged tissue. For immune-mediated diseases, systemic administration of stem cells can modulate the immune system. The earliest clinical work has been with autologous stem cell sources, such as adipose tissue and bone marrow. In immune-mediated diseases, the MSCs are used to downregulate production of inflammatory cytokines and to block T-cell activation. Cells are generally given intravenously. Multiple sclerosis, rheumatoid arthritis and lupus have been successfully treated in human clinical trials. Mesenchymal stem cells can also stimulate resident local cells, such as keratinocytes and progenitor cells, to proliferate, migrate and repair skin injury and disease.

Looking ahead – The discovery of the MSC in adipose tissue has spawned a global effort to utilize these cells in therapy of a wide range of diseases of the skin. Reconstructive surgery, scar blocking and resolution and skin regeneration have all been shown to be possible in human and animal studies.

Introduction

Stem cell therapy is not a new discipline. The first stem cell transplants were performed in the 1950s using bone marrow to reconstitute the marrow of chemotherapy patients.[1] These stem cells were primarily haematopoietic and were used to replace the damaged or dead marrow stem cells so that the patient could replenish the white and red cell lineages. In the 1980s, a new subpopulation of marrow cells was discovered and named the mesenchymal stem cells (MSCs), in the belief that this cell type was from the mesenchyme and could be induced to differentiate into a mesenchymal tissue cell type, such as bone or cartilage.[2] In the ensuing decades, stem/progenitor cells have been identified in nearly every tissue of the body. In 1998, James Thompson at the University of Wisconsin was the first researcher to isolate and propagate human embryonic stem cells (ESCs) and ushered in the era of 'stem cell medicine'. Although thought to be the most pleuripotent stem cell, the ESC has not yet proved to be a clinically useful cell type, owing to major risks of tumourigenesis and immune rejection.[3] On the contrary, the adult MSC has been shown to be nontumourigenic and nonimmunogenic. The clinical interest in MSCs has focused on their ability to modulate the immune system, to stimulate tissue regeneration and to differentiate into all three germ layer lineages. *In vitro* models, preclinical animal models and early clinical translation provide evidence that stem cells can prove to be safe and efficacious in the therapy of dermatological conditions in human and veterinary medicine. This review chronicles the progression of basic and clinical research in support of the clinical use of the MSC.

Sources and types of stem cells

What are stem cells? In traditional textbooks, it was taught that stem cells were the origin of all major tissue types and that once cells became partly or totally differentiated into a cell type they were now terminal cells and could not dedifferentiate. It is now known that cells are very 'plastic' and can transform more than originally thought.[4] As usual, the situation is much more intricate and complicated than the initial studies indicated. Table 1 summarizes the characteristics of several classes of stem cells. There are two major types of stem cells, the ESCs and adult stem cells (ASCs). Embryonic stem cells come from the inner cell mass of an early embryo. Once removed, they can be grown *in vitro* and are generally immortal in cell culture. They can be induced *in vitro* to form a very large number of cell/tissue types; however, their nature is to form a whole organism. In research, they are already a very powerful tool in the discovery of mechanisms of healing, disease pathogenesis and organ formation. However, to the clinician, they still have two very critical flaws that block their use in the clinic, as

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Table 1. A summary of stem cell types and general characteristics

Characteristics	Adult stem cell*	Embryonic stem cell	Induced pluripotent stem cell
Sources	Fat, bone marrow, cord blood or other tissues	Inner cell mass of an early embryo	Adult stem cell genetically modified to act like embryonic stem cell
Form teratomas	No	Yes	Yes
Rejected as foreign tissue	No	Yes	Yes
Self-renewal	Yes	Yes	Yes
Differentiation capacity	Yes	Yes	Yes
Immortal cell lines	No	Yes	Yes

*A specific type of adult stem cell, the mesenchymal stem cell, is found in mesenchymal tissues, such as bone marrow and adipose tissue.

follows: (i) they form teratomas when implanted into a patient; and (ii) they are a foreign genotype and can potentially be rejected by the recipient's immune system.[3] In addition, there is a major controversy about the use of embryos to harvest these cells.

Adult stem cells are different from ESCs. They are found in almost every tissue of every human and animal and are used by the body to make repairs in everyday life. Some of these stem cells, particularly MSCs, have the ability to produce large amounts of growth factors and can differentiate into many body tissues. They do not form teratomas when injected into patients unless they have been damaged in the laboratory and, if they are from the same patient (autologous), they will not be rejected as foreign. Neonatal stem cells from the placenta, umbilical cord, amnion, etc. are generally considered to be ASCs, because they behave in the manner described above. Induced pleuripotent stem cells are adult cells that have been genetically reprogrammed to revert to a more undifferentiated state. Like ESCs, they can form teratomas and they have also recently been reported to be immunogenic, even if the source of adult cells is from the same patient.[5]

What are the sources of adult stem cells? They are found in nearly every tissue, including bone marrow, fat, skin, nerve tissue, muscle and many others. If the source is from a different species than the recipient (e.g. pig valves for people) they are called xenogeneic. If they are from the same species but a different individual (e.g. kidney for transplant) they are called allogeneic. If the donor is the recipient then they are termed autologous. The only tissue with adequate concentrations of ASCs for direct (uncultured) use is the adipose depot. All other sources need to be expanded *ex vivo* in order to have a therapeutic dosage available to treat a patient.

An interesting canine stem cell source was recently identified in the hair follicle bulge.[6] Human bulge stem cells have been previously identified, but this is the first verification that there are canine bulge stem cells that share many characteristics with the human bulge cells. This bulge region is found as a subtle swelling of the outer root sheath in both the canine and human hair follicle, near the insertion point of the arrector pili muscle.[6] The stem cells were found using labelling techniques at this site during anagen phase, but also in the secondary germ at the bottom of the follicle during telogen, leading to the hypothesis that these are the cells responsible for regeneration of the dermal component of hair follicles during cycling.[6] Further discussion of the canine bulge stem cell will be covered in the section on alopecia below.

Identification and characterization of the mesenchymal stem cell

Although there is no single 'marker' or identifying characteristic that clearly identifies the MSC, there are a combination of characteristics that are generally accepted to be representative of this cell type. The International Society of Cell Therapy has published their guidelines on the characterization of the MSC.[7] The proposed primary characteristics are as follows: (i) the MSC must be plastic adherent when maintained in standard culture conditions; (ii) the MSC must express cell surface markers CD105, CD73 and CD90; lack expression of CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR surface molecules; and (iii) the MSC must be capable of differentiating into osteoblasts, adipocytes and chondroblasts *in vitro*. Although stem cell scientists continue to develop more stringent criteria, these basic criteria are generally accepted as the baseline for declaring a cell type as a MSC.

Figure 1 demonstrates the third primary characteristic of the MSC, namely differentiation. These four photomicrographs show adipogenic, chondrogenic, neurogenic and osteogenic differentiation of adipose-derived stem cells (ADSCs).[8]

Additionally, researchers use gene arrays to evaluate whether the cell type in question is able to express the genes thought to be related to the abilities of stem cells. Common genes expressed in progenitor cells include nerve growth factor receptor, basic fibroblast growth factor 2, frizzled homolog 9 and activated leukocyte cell adhesion molecule. In a recent publication, the authors used these genes in a dolphin skin regeneration clinical study to verify that the cells of interest expressed these genes.[8] The International Society of Cell Therapy has not adopted any gene array criteria for MSCs at this time.

Mechanisms of action of the mesenchymal stem cell

In contrast to drug or growth factor therapy, stem cell therapy does not rely upon a single target receptor or a single pathway for its action. In stem cell therapy, the ASCs are delivered either directly to the area of trauma or disease (e.g. wounds, tendonitis or osteoarthritis) or are

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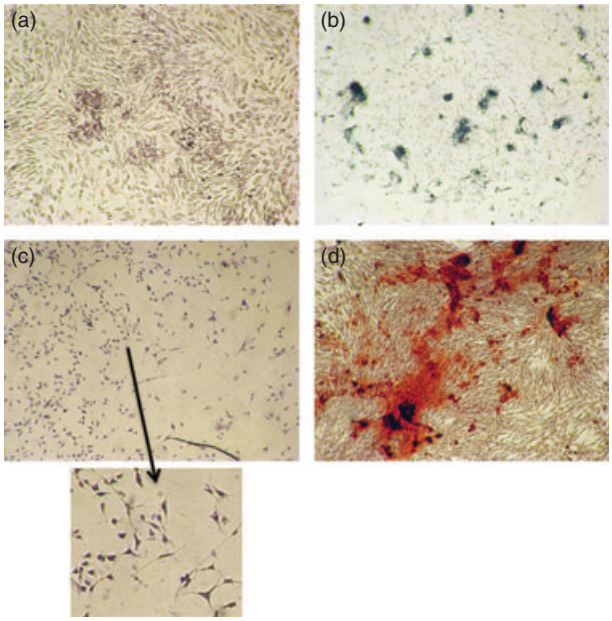

Figure 1. Photomicrographs of positive differentiation assays for the following adipose-derived stem cells: adipogenic (a); chondrogenic (b); neurogenic (c); and osteogenic (d). The inset photomicrograph below (c) is a higher magnification view of the neurogenic differentiation slide showing the typical neuronal phenotype. This study used standardized induction media known to induce each specific phenotype, and immunostaining was not employed (by courtesy of Vet-Stem, Inc., Poway, CA, USA).

delivered systemically (e.g. liver disease, renal disease or immune-mediated disease). Both delivery methods take advantage of the ability of stem cells to differentiate into many tissue types and their ability to 'communicate' with the cells of their local environment through paracrine modalities to create the optimal environment for natural healing.[4]

While therapeutically successful, the detailed molecular mechanisms of stem cell-related healing are complex and remain under investigation. Repair occurs through a complex variety of demonstrated stem cell functions, including the following: (i) trophic support;[4,9,10] (ii) - anti-inflammatory and immunomodulatory functions;[11,12] (iii) revascularization;[13] (iv) anti-apoptotic activity;[13] (v) differentiating capacity;[14] and (vi) homing.[15] Although the mechanisms remain under investigation, clinical efficacy is documented in preclinical human and animal trials.[16] The public have long used aspirin to decrease fever and control pain, beginning in the late 1800s, but the mechanisms of action were not discovered until 1971 when British pharmacologist John Robert Vane discovered the suppression of prostaglandins and received the Nobel Prize in 1981.[17]

Stem cell therapy delivers a population of cells able to communicate with other cells in their local environment. Until recently, differentiation was thought to be the primary function of stem cells. However, the functions of regenerative cells are now known to be much more diverse, including immune modulation[18] and secretion of cell signalling factors and cytokines that influence both local and remote cell populations.[4] These cellular functions are implicated in a highly integrated and complex network. Cellular therapy should be viewed as a complex, yet balanced, approach to a therapeutic goal where the cells take their signals from the microenvironment of the injured tissue. Unlike traditional medicine, in which one drug targets one or a few receptors, a single stem cell therapy can be applied in a wide variety of injuries and diseases.

Trophic support

Multiple studies demonstrate that ASCs secrete bioactive levels of cytokines and growth factors that support angiogenesis, tissue remodelling, differentiation and anti-apoptotic events.[10,13] Adipose and bone marrow stem cells secrete a number of angiogenesis-related cytokines, such as vascular endothelial growth factor, hepatocyte growth factor, basic fibroblast growth factor, granulocyte–macrophage colony-stimulating factor and transforming growth factor-β.[10,13]

Anti-inflammatory/immunomodulatory functions

In general, *in vitro* studies demonstrate that bone marrow stem cells (BMSCs) and ADSCs limit inflammatory responses and promote anti-inflammatory pathways. When present in an inflammatory environment, BMSCs may alter the cytokine secretion profile of dendritic cell subsets and T-cell subsets, causing a shift from a pro-inflammatory environment to an anti-inflammatory or tolerant environment.[12] Bone marrow stem cells and ADSCs do not express MHC class II antigens or costimulatory molecules and they suppress T-cell proliferation.[19] Adult stem cells suppress mixed lymphocyte reactions and inhibit T-cell proliferation induced by a third cell type or by mitogenic factors.[20] Both types of stem cells are able to control lethal graft-versus-host disease that occurs in mice after haploidentical haematopoietic transplantation.[18,20]

Revascularization

The stromal vascular fraction extracted from adipose tissue contains ADSCs and endothelial progenitor cells that promote angiogenesis and neovascularization by the secretion of cytokines, such as hepatocyte growth factor, vascular endothelial growth factor, placental growth factor, transforming growth factor, fibroblast growth factor and angiopoietin.[21] In an *in vivo* model of hindlimb ischaemia, intravenous injection of ADSCs was associated with an increase in blood flow and vascular density and incorporation of the cells in the leg vasculature.[22]

Anti-apoptosis

Apoptosis is defined as a programmed cell death or 'cell suicide', an event that is genetically controlled. In normal conditions, apoptosis determines the lifespan and coordinated removal of cells. When acutely injured tissue is denied critical blood flow, ischaemia will result. Adipose-derived stem cells significantly reduced endothelial cell apoptosis during ischaemic events in animal studies.[13] Rehman *et al.*[13] demonstrated that ADSCs express factors that support cell survival and avoid apoptosis.

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Differentiating capacity

Studies using stem cells from a variety of sources demonstrate a diverse plasticity, including differentiation into adipogenic, osteogenic, chondrogenic, myogenic, cardiomyogenic, endothelial, hepatogenic, neurogenic, epithelial and haematopoietic lineages.[4] These data are supported by *in vivo* experiments and functional studies that demonstrated the regenerative capacity of stem cells to repair damaged or diseased tissue via transplant engraftment and differentiation.[23] Nixon *et al.*[24] demonstrated statistically significant improvement in histological repair of a collagenase-induced injury in the superficial digital flexor tendon in horses treated with autologous regenerative cells harvested from fat.

Homing

Homing (chemotaxis) is an event by which a cell migrates from one area of the body to a distant site, where it may be needed for a given physiological event. Homing is an important function of adult stem cells and one mechanism by which intravenous or parenteral administration of MSCs permits a therapeutic cell to target a specific diseased area effectively. A cerebral arterial occlusion model of stroke demonstrated that labelled BMSCs administered intravenously 24 h and 7 days postinjury migrated to the area of injury, dramatically reducing the stroke infarct size.[25] Mesenchymal stem cells homed to the lung in response to injury and reduced inflammation and collagen deposition in a mouse model of pulmonary fibrosis.[26]

The mechanism of how stem cells home to injured tissues and migrate across endothelium is not fully understood. It is likely that injured tissues express specific receptors for chemokines and ligands to facilitate trafficking, adhesion and infiltration of stem cells, as is the case with recruitment of leukocytes to sites of inflammation. Chemokines and adhesion molecules play a significant role in the trafficking of leukocytes, and BMSCs have been shown to express some of these molecules.[15]

Engineered skin

The discipline of tissue engineering attempts to use scaffolding and cells to create a tissue construct, grown *ex-vivo*. In the case of skin, the construct can be epidermis, dermis or some combination, to create a transplantable tissue. This engineered tissue can be used in place of autografts or noncellular scaffolding to repair damaged skin, such as in trauma, burns or ischaemic tissue. The largest barrier to the successful transplantation of engineered skin is vascularization. An epidermal graft must be nourished by the passive diffusion of nutrients from dermal capillaries. Early studies by Boyce[27] demonstrated that engineered grafts required 10–15 days before dermal capillaries could effectively form. This length of time is not compatible with graft survival. Adipose-derived stem cells co-cultured with human fibroblasts can create a vascularized skin construct.[28] This type of construct shows the use of the revascularization capability of stem cells in a combination engineered graft.

Although there are no commercially available canine, equine or feline tissue-engineered products, the human market gives evidence that such grafts are possible, practical and commercially successful (Dermagraft; Advanced Biohealing, Westport, CT, USA, recently purchased by Shire Pharmaceuticals). Dermagraft provides neonatal tissue-derived fibroblasts cultured on a degradable matrix.

Mesenchymal stem cell therapy of chronic nonhealing wounds

Healing of wounds requires the coordination of cell migration, cellular proliferation and differentiation and the assembly of scaffolding (extracellular matrix). Additionally, angiogenesis is required to create the vascular supply route. Typically, a granulation bed forms, and re-epithelialization occurs. In chronic wounds, a dysregulation occurs, resulting in a wound that does not heal by the normal course. As described in the preceding subsections, stem cells have the ability to home to areas of inflammation, interact with the local microenvironment, attract other progenitor cells, differentiate into various tissues types and produce a wide variety of cytokines and growth factors that could influence healing in a chronic wound. Human ADSCs can influence the migration and proliferation of human dermal fibroblasts and, in rodent models, can reduce the time for wound closure.[29]

A number of rodent models have shown that MSCs applied intravenously,[30] topically[31] and subcutaneously[32] can improve wound healing. Human clinical studies have demonstrated the healing of chronic fistulas in patients with Crohn's disease, both by local delivery and by the intravenous route.[33] Reports on the clinical application of BMSCs in human wound therapies have demonstrated that grafted MSCs facilitate skin regeneration, both in acute and in chronic wounds.[34–36] Falanga *et al.*[35] used autologous bone marrow MSCs delivered in a fibrin spray to accelerate healing in human cutaneous wounds.

In a recent study, standardized skin wounds in the dolphin (*Turchiops truncates*) were treated with cultured ADSCs in a blinded, placebo-controlled clinical study.[8] Wound tissue biopsy samples were evaluated by a blinded, independent histopathologist, with analysis of cell proliferation (number of mitoses) and healing rate on days 1, 5 and 15 after treatment. Wounds in dolphins treated with autologous ADSCs showed improved healing compared with the saline placebo-treated dolphins (Figure 2).[8]

Mesenchymal stem cell therapy of immune-mediated skin diseases

MSC populations have the ability to modulate the immune system as described in the mechanisms of action section above. In particular, they have the ability to suppress T-cell alloreactivity. In patients with transplant rejection graft-versus-host disease, MSCs have shown the ability to suppress the activated T cells and to prevent activation of the T cells. This phenomenon has been used to prolong skin graft survival[37] and in the treatment of severe graft-versus-host disease.[38]

Atopic dermatitis is a complicated disease. Atopy is defined as the heritable predisposition of the production of IgE to otherwise ordinary environmental substances, such as pollens, moulds and house dust mites.[39] There is

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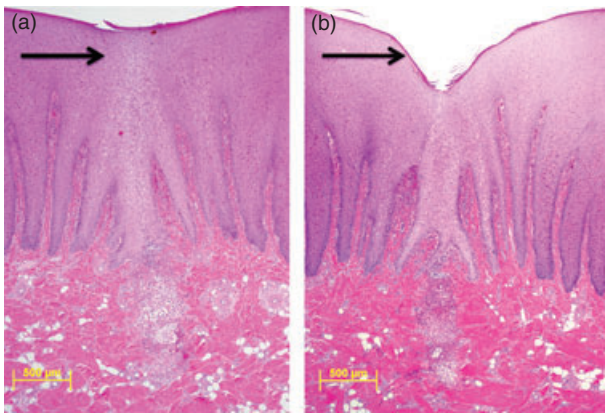

Figure 2. Dolphin skin wound biopsy samples obtained on day 15 after intralesional treatment with adipose-derived cultured autologous stem cells (a) and phosphate-buffered saline (b). There was improved healing in the stem cell-treated group. The arrows show the site of the original wound and illustrate the superior filling in the treated versus control lesion.

evidence to support transcutaneous presentation of allergen both to initiate and to perpetuate atopic inflammation and pruritus.[40] When present in an inflammatory environment, data demonstrate that MSCs may alter the cytokine secretion profile of dendritic cell subsets and T-cell subsets, causing a shift from a pro-inflammatory environment to an anti-inflammatory or tolerant environment.[12] Mesenchymal stem cells do not express MHC class II antigens or costimulatory molecules and they suppress T-cell proliferation.[20] Adipose-derived stem cells suppress mixed lymphocyte reactions and inhibit T-cell proliferation induced by a third cell type or by mitogenic factors.[20] Additionally, BMSCs and ADSCs suppress T-cell activation.[41]

Most recently, Riordan *et al.*[42] reported on ADSC therapy of multiple sclerosis patients and reviewed the literature on the cells from the vascular stromal fraction and their function in modulation of inflammation and autoimmunity. Kang *et al.*[43] replicated much of this proof of immunomodulation of the stem cell using canine ADSCs, showing that the dog has a similar MSC to other reported species. Taken together, these data support the idea that ASCs could provide the immunoregulation necessary to control atopic dermatitis in dogs. The only published data on canine stem cell therapy are from a small pilot study using a small adipose biopsy and cell culture.[44] This study used autologous stem cells and the intravenous route, with no statistical improvement in clinical signs of atopic dermatitis. On the contrary, Liang *et al.*,[45] in a human clinical study, showed improvement in the cutaneous clinical redundant signs of refractory lupus when treated with allogeneic MSCs.

Mesenchymal stem cell therapy of scar tissue

The MSC has been shown to produce hepatocyte growth factor, a basic fibroblast growth factor that can inhibit scar tissue formation.[46] In human plastic surgery, it is reported that ADSCs, or even the stromal vascular fraction processed from lipoaspirate, have the ability to block or remodel scar tissue when used alone or in conjunction with a fat graft.[47] In models of liver disease in rodents, MSC infusion can modulate metalloproteinase activity and reduce deposition of collagen, reducing the fibrosis seen with histopathology.[48] Lung fibrosis can also be blocked by MSC infusion in the bleomycin model of pulmonary fibrosis and the mechanisms appear to include blockade of interleukin-1 and tumour necrosis factor-α.[26]

Mesenchymal stem cell therapy in alopecia

There is a cyclical regeneration of hair follicles during the life of an animal that is believed to be modulated by stem cells.[49] Kobayashi *et al.*[6] reported the similarity of the canine and human bulge cells and was able to show multipotency of these cells in the reconstitution of pilosebaceous glands. Immunohistochemistry of the bulge region in canine skin samples demonstrated a population of CD34 glycoprotein-positive cells.[50] This marker is most commonly found on the surface of haematopoietic stem cells. The best approach for therapy of alopecia has been debated. Options include using cytokines to stimulate these resident multipotent cells, injection of cultured bulge cells and injection of a MSC preparation that might stimulate activity of these resident progenitors.

The large size of the market for therapy for human male pattern baldness has spawned a number of biotechnology companies that are employing these various approaches to treatment. Dermal papilla cells are thought to be a major regulator of the keratinocytes and hair growth.[51] At least one company (Intercytex, Manchester, UK) has entered human clinical testing with autologous cultured dermal papilla cells and fibroblasts, based upon preclinical data showing that this approach can stimulate new hair growth. Replicel Life Science (Vancouver, BC, Canada) has taken a similar approach but uses autologous dermal sheath cup cells and has also entered human clinical testing. Bone marrow stem cells and umbilical cord stem cells have been employed *in vitro* and in an athymic nude mouse model to create dermal papilla-like structures and hair follicles.[52] The general concepts of paracrine anti-inflammatory and mitotic effects of ASCs already discussed could be employed in strategies to heal and stimulate the damaged bulge and related cells in patients with alopecia. Furthermore, autoimmune damage to the hair follicle region might be treated using the ability of stem cells to reduce T-cell activation and cause activated T cells to become apoptotic.[20,43]

Bulge stem cell markers in oncology

In a letter to the editor of *Veterinary Dermatology*, Grandi *et al.* [53] noted that use of immunohistochemical markers found on bulge stem cells might help to elucidate the histogenesis of certain tumours. In particular, ceratokeratin (CK15), CD34 and nestin have been reported in the veterinary literature.[6,50,54,55] An example of a study of human tumours found CD15-positive cells in trichoepitheliomas and certain basal cell carcinomas, while squamous cell carcinomas were negative.[56] Further investigation of these markers and others markers found on bulge stem cells needs to be performed on veterinary tumours. In

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contrast to the suggestive literature on bulge stem cells above, the MSC literature has not reported tumour formation in association with MSC clinical therapy.[57]

US Food and Drug Administration (FDA) regulation of stem cell therapy in veterinary medicine

In the USA, the FDA Centre for Veterinary Medicine regulates all veterinary drugs. Stem cell products are considered to be drugs and are regulated as such by the FDA.[58] Service businesses are being allowed to operate under regulatory discretion at the present time, but any products, such as allogeneic cells, must be approved under the New Animal Drug Approval (NADA process) according to Lynne Oliver of the FDA, Centre for Veterinary Medicine.[59]

Future perspectives of stem cell therapy in veterinary dermatology

It is clear from the substantial amount of research, both past and ongoing, that there will be translation of basic research into clinical protocols in the coming years. Current clinical practices in human dermatology will be likely to find their way into veterinary medicine, as have many other clinical practices. The prospect of MSC use in therapy of veterinary dermatological conditions is promising and we await appropriate clinical studies to provide guidance for clinical use. The veterinary species will continue to provide sound data that can be used to further the approval process for translation into the human clinics. 'One Medicine' is truly a partnership between human and veterinary medicine, with the goal of improvement of the health of human and veterinary patients.

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Résumé

Contexte – Les cellules souches adultes viennent de plusieurs sources et ont la capacité de se différencier en plusieurs types cellulaires y compris ceux de la peau. Les cellules souches les plus fréquemment étudiées sont celles appelées cellules souches mésenchymateuses (MSCs), qui sont facilement isolées de la moelle osseuse et du tissu adipeux. Les cellules souches mésenchymateuses sont connues pour produire un large éventail de cytokines qui régulent le processus de régénération. La facilité de prélèvement, de propagation et d'utilisation de ces MSCs dans le traitement des dermatoses traumatiques, ischémiques et à médiation immune est émergente.

Approche et preuve – Dans les dermatoses traumatiques et ischémiques, les MSCs sont utilisées en ingénierie tissulaire cutanée et par injection directe dans les tissus lésés. Pour les maladies à médiation immune, l'administration systémique de cellules souches peut réguler le système immunitaire. Un travail clinique précédent a été réalisé avec des sources de cellules souches autologues, comme le tissu adipeux ou la moelle osseuse. Dans les maladies à médiation immune, les MSCs sont utilisées pour diminuer la production de cytokines inflammatoires et pour bloquer l'activation des cellules T. Les cellules sont généralement administrées en intraveineuse. Les scléroses multiples, l'arthrite rhumatoïde et le lupus ont été traités avec succès dans des études cliniques humaines. Les cellules souches mésenchymateuses peuvent aussi stimuler les cellules locales résidentes telles que les kératinocytes et les cellules progénitrices, pour proliférer, migrer et réparer les dommages et les maladies de la peau.

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Perspective d'avenir – La découverte des MSC dans le tissu adipeux a donné naissance à un effort mondial pour utiliser ces cellules dans le traitement d'un large éventail de dermatoses. La chirurgie reconstructrice, la cicatrisation et la régénération cutanée se sont toutes avérées possibles dans les études humaines et animales.

Resumen

Introducción – Células madre adultas provienen de muchas fuentes y tienen la capacidad de diferenciarse en muchos tipos celulares, incluyendo los de la piel. Las células madre mas comúnmente estudiadas son las denominadas células madre mesenquimales (MSCs), que se aíslan fácilmente a partir de médula ósea y tejido adiposo. Las células madre mesenchimales pueden producir una variedad de citoquinas que modulan el proceso de regeneración. La facilidad para su aislamiento, propagación y uso de estas MSCs en el tratamiento de procesos traumáticos, isquémicos e inmunomediados de la piel esta emergiendo.

Aproximación y evidencia – en el daño traumático e isquémico de la piel, MSCs se utilizan en piel creada por ingeniería de tejidos y mediante la inyección directa en el tejido dañado. En el caso de la enfermedades inmunomediadas, la administración sistémica de células madre puede modular el sistema inmune. El trabajo clínico inicial ha sido con células madres autólogas de tejidos tales como tejido adiposo y médula ósea. En enfermedades inmunomediadas las MSCs se utilizan para disminuir la producción de citoquinas inflamatorias y bloquear la activación de linfocitos T. Las células son generalmente administradas por vía intravenosa. En ensayos en seres humanos se han tratado con éxito la esclerosis múltiple, la artritis reumatoide y el lupus. Las células madre mesenquimales también pueden estimular las células locales residentes, tales como los queratinocitos y células progenitoras, a proliferar, migrar y reparar los daños en la piel y las enfermedades.

Mirando hacia delante – El descubrimiento de las MSCs en el tejido adiposo ha creado un esfuerzo global para utilizar estas células en el tratamiento de un amplio rango de enfermedades de la piel. Cirugía reconstructiva, bloqueo y resolución de la cicatrización y regeneración de la piel han sido ya posibles en estudios en personas y animales.

Zusammenfassung

Hintergrund – Adulte Stammzellen kommen aus vielen Quellen und haben die Kapazität, sich in viele verschiedene Zelltypen – sowie auch in Zellen der Haut - zu differenzieren. Die am weitesten untersuchten Stammzellen sind die so genannten mesenchymalen Stammzellen (MSCs), die aus Knochenmark und Fettgewebe leicht isoliert werden können. Mesenchymale Stammzellen sind dafür bekannt, dass sie eine Vielzahl an Zytokinen produzieren, die den Regenerationsprozess modulieren. Die Leichtigkeit der Gewinnung, der Vermehrung und der Verwendung dieser MSCs bei der Behandlung von traumatischen, ischämischen und immun-mediierten Hautproblemen wird mehr und mehr bekannt.

Herangehensweise und Evidenz – Bei traumatischer und ischämischer Verletzung der Haut werden MSCs in gewebetechnisch hergestellter Haut verwendet und direkt in zerstörtes Gewebe injiziert. Bei immun-mediierten Erkrankungen kann die systemische Administration von Stammzellen das Immunsystem modulieren. Die früheste klinische Arbeit wurde mit autologen Stammzellquellen, so wie Fettgewebe und Knochenmark, durchgeführt. Bei immun-mediierten Erkrankungen werden die MSCs verwendet, um die Produktion der entzündlichen Zytokine zu erniedrigen und um die T-Zell Aktivierung zu blockieren. Die Zellen werden normalerweise intravenös verabreicht. Multiple Sklerose, rheumatoide Arthritis und Lupus sind in klinischen Versuchsreihen beim Menschen erfolgreich behandelt worden. Mesenchymale Stammzellen können auch lokale Zellen, wie Keratinozyten und Progenitorzellen stimulieren, um in der Folge zu proliferieren, zu wandern und Hautverletzung und Krankheit zu reparieren.

Blick in die Zukunft – Die Entdeckung der MSC in Fettgewebe hat ein globales Bestreben ausgelöst, diese Zellen bei der Therapie einer ganzen Reihe von Hauterkrankungen zu verwenden. Wiederherstellungschirurgie, Verhinderung von Narbenbildung und die Wiederherstellung und die Regeneration der Haut haben sich sowohl in Studien beim Menschen als auch bei Tieren als möglich herausgestellt.

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要約

背景 – 成熟した幹細胞は様々な起源から発生し、皮膚を含め様々な細胞のタイプに分化する能力を持つ。最も一般的に研究されている幹細胞は骨髄や脂肪組織から簡単に分離される間葉系幹細胞（MSCs）と定義されるものである。間葉系幹細胞は再生過程を調節する多くのサイトカインを産生する。外傷性、虚血性、免疫介在性皮膚疾患の治療における MSCs の使いやすさ、回収しやすさ、増殖しやすさが明らかになりつつある。

アプローチと証拠 – 外傷性と虚血性皮膚障害で、MSCs は傷ついた組織に直接注入することにより組織-人工皮膚として働く。免疫介在性疾患では、幹細胞を全身投与すると免疫システムを調整する。初期の臨床研究では自己幹細胞起源の脂肪組織や骨髄などが材料として使われてきた。免疫介在性疾患では MSCs は炎症性サイトカインの産生の抑制や T 細胞活性を抑制する目的で使用されている。細胞は一般的に静脈投与で投与される。ヒトの臨床治験で、多発性硬化症、関節リュウマチ、ループスの治療に成功した。間葉系幹細胞は増殖、遊走し皮膚損傷や疾患を修復するためのケラチノサイトや前駆細胞などの局所に存在する細胞を刺激する。

展望 – 脂肪組織における MSC の発見はこれらの細胞を幅広い範囲の皮膚疾患の治療に活用するグローバルな取り組みを生み出した。再建手術、瘢痕の阻止と消失、皮膚の再生の全てがヒトと動物の研究で可能であることが示されている。

摘要

背景 – 成体干细胞有许多来源，有能力分化为包括皮肤等多种细胞类型。最常见的干细胞研究是那些所谓间充质干细胞（MSCs），它们很容易从骨髓和脂肪组织中分离。间充质干细胞已知可产生大批调节再生过程的细胞因子。由于这些 MSCs 容易被收集、制备和使用，常用于治疗外伤性、缺血性和免疫介导性皮肤病。

方法和证据 – 在外伤性和缺血性皮肤损伤中，MSCs 用于皮肤组织工程并直接注入到损伤组织中。对于免疫介导性疾病，全身使用自体干细胞可调节免疫系统。最早的临床工作中的自体干细胞来源于如脂肪组织和骨髓。在免疫介导性疾病中，MSCs 用于抑制炎性细胞因子产生并阻止 T-细胞激活。一般通过静脉注射给予细胞。在人的临床试验中成功治愈了多发性硬化症、风湿性关节炎和狼疮。间充质干细胞也可刺激局部常驻细胞，如角质形成细胞和祖细胞的增殖、移动、修复皮肤损伤和疾病。

前瞻 – MSC在脂肪组织中的发现引发了全球利用这些细胞治疗多种皮肤病的热潮。重建外科、疤痕填塞和消除，以及皮肤再生的可能性在人和动物的研究中都已证明。

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