--morphogen

Turing coined the term ‘morphogen’ to signify biochemical substances that diffuse between cells and generate specific responses at particular concentrations <http://rstb.royalsocietypublishing.org/content/royptb/237/641/37.full.pdf>

<http://dev.biologists.org/content/131/4/703>

----MSC

MSCs were originally identified by Friedenstein in mouse bone marrow and were characterized according to their multilineage potential[1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4320647/" \l "R1)–[3](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4320647/" \l "R3). Caplan later referred to these cells as mesenchymal stem cells[4](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4320647/" \l "R4), yet to date rigorous in vivo demonstration of their stem cell properties has not been established. As a result of their original identification in the bone marrow, many referred to them as “bone marrow stromal cells.” However, MSCs have since been shown to be derived from both pericytes and adventitial progenitor cells from nearly all tissues[5](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4320647/" \l "R5),[6](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4320647/" \l "R6). Thus it may be appropriate to refer to MSCs as “multipotent perivascular-derived cells.” ----------- Ankrum JA, Ong JF, Karp JM (2014). ["Mesenchymal stem cells: immune evasive, not immune privileged"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4320647). Nature Biotechnology. 32 (3): 252–60. [doi](https://en.wikipedia.org/wiki/Digital_object_identifier" \o "Digital object identifier):[10.1038/nbt.2816](https://doi.org/10.1038/nbt.2816). [PMC](https://en.wikipedia.org/wiki/PubMed_Central" \o "PubMed Central) [4320647](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4320647) Freely accessible. [PMID](https://en.wikipedia.org/wiki/PubMed_Identifier" \o "PubMed Identifier) [24561556](https://www.ncbi.nlm.nih.gov/pubmed/24561556)

However, a variety of mesenchymal-like stem cells (MSCs) residing in skeletal muscle also contribute to repair in response to damage. These mononuclear cells have been isolated and categorized as multipotent muscle-derived stem cells (MDSC) [[5]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256189/" \l "pone.0029760-Qu1), [[6]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256189/" \l "pone.0029760-QuPetersen1), side population (SP) cells [[4]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256189/" \l "pone.0029760-Motohashi1), [[7]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256189/" \l "pone.0029760-Gussoni1)–[[9]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256189/" \l "pone.0029760-Uezumi1), muscle resident progenitor cells [[10]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256189/" \l "pone.0029760-Mitchell1), mesoangioblasts [[2]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256189/" \l "pone.0029760-Sampaolesi1) and pericytes [[3]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256189/" \l "pone.0029760-Dellavalle1) based on method of extraction, localization within muscle, cellular function, and heterogeneous cell surface markers. Despite the inability to clearly and efficiently distinguish among the different adult stem cell populations, stem cell antigen-1 (Sca-1)/lymphocyte antigen 6 (Ly-6A) is a commonly expressed murine glycosyl phosphatidylinositol-anchored cell surface protein that is used in combination with other cell surface markers to identify MSCs in muscle. The majority of isolated Sca-1+ MSCs do not express myogenic markers (Pax7, MyoD) and vary in their ability to spontaneously differentiate into skeletal muscle [[1]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256189/" \l "pone.0029760-Asakura1), [[3]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256189/" \l "pone.0029760-Dellavalle1), [[9]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256189/" \l "pone.0029760-Uezumi1)–[[11]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256189/" \l "pone.0029760-Tamaki1), yet can readily fuse with myoblasts in co-cultures and/or can secrete factors that potently activate satellite cells in response to injury or disease -------- Valero MC, Huntsman HD, Liu J, Zou K, Boppart MD (2012). ["Eccentric exercise facilitates mesenchymal stem cell appearance in skeletal muscle"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256189). *PLoS ONE*. 7 (1): e29760. [doi](https://en.wikipedia.org/wiki/Digital_object_identifier" \o "Digital object identifier):[10.1371/journal.pone.0029760](https://doi.org/10.1371/journal.pone.0029760). [PMC](https://en.wikipedia.org/wiki/PubMed_Central" \o "PubMed Central) [3256189](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256189) Freely accessible. [PMID](https://en.wikipedia.org/wiki/PubMed_Identifier" \o "PubMed Identifier) [22253772](https://www.ncbi.nlm.nih.gov/pubmed/22253772)

MSCs, the multilineage stem cells, differentiate only to tissue of mesodermal origin, which includes tendons, bone, cartilage, ligaments, muscles, and neurons [[50](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/" \l "B50)]. MSCs are the cells which express combination of markers: CD73+, CD90+, CD105+, CD11b−, CD14−, CD19−, CD34−, CD45−, CD79a−, and HLA-DR, reviewed elsewhere [[50](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/" \l "B50)]. The application of MSCs in regenerative medicine can be generalized from ongoing clinical trials, phasing through different state of completions, reviewed elsewhere [[90](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/" \l "B51)]. This section of review outlines the most recent representative applications of MSCs ([Figure 4](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/figure/fig4/" \t "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/figure); [Table 1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/table/tab1/" \t "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/true)). The anatomical and physiological characteristics of both donor and receiver have equal impact on therapeutic outcomes. The bone marrow derived MSCs (BMDMSCs) from baboon are morphologically and phenotypically similar to those of bladder stem cells and can be used in regeneration of bladder tissue. The BMDMSCs (CD105+, CD73+, CD34−, and CD45−), expressing GFP reporter, coaxed with small intestinal submucosa (SIS) scaffolds, augment healing of degenerated bladder tissue within 10 wks of the transplantation [[51](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/" \l "B52)]. The combinatorial CD characterized MACs are functionally active at transplantation site, which suggests that CD characterization of donor MSCs yields superior regenerative outcomes [[51](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/" \l "B52)]. MSCs also have potential to regenerate liver tissue and treat liver cirrhosis, reviewed elsewhere [[91](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/" \l "B53)]. The regenerative medicinal application of MSCs utilizes cells in two formats as direct transplantation or first transdifferentiation and then transplantation; ex vivo transdifferentiation of MSCs deploys retroviral delivery system that can cause oncogenic effect on cells. Nonviral, NanoScript technology, comprising utility of transcription factors (TFs) functionalized gold nanoparticles, can target specific regulatory site in the genome effectively and direct differentiation of MSCs into another cell fate, depending on regime of TFs. For example, myogenic regulatory factor containing NanoScript-MRF differentiates the adipose tissue derived MSCs into muscle cells [[92](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/" \l "B54)]. The multipotency characteristics represent MSCs as promising candidate for obtaining stable tissue constructs through coaxed 3D organoid culture; however heterogeneous distribution of MSCs slows down cell proliferation, rendering therapeutic applications of MSCs. Adopting two-step culture system for MSCs can yield homogeneous distribution of MSCs in biomaterial scaffolds. For example, fetal-MSCs coaxed in biomaterial when cultured first in rotating bioreactor followed with static culture lead to homogeneous distribution of MSCs in ECM components [[7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/" \l "B7)]. Occurrence of dental carries, periodontal disease, and tooth injury can impact individual's health, where bioengineering of teeth can be the alternative option. Coaxing of epithelial-MSCs with dental stem cells into synthetic polymer gives rise to mature teeth unit, which consisted of mature teeth and oral tissue, offering multiple regenerative therapeutics, reviewed elsewhere [[52](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/" \l "B55)]. Like the tooth decay, both human and animals are prone to orthopedic injuries, affecting bones, joint, tendon, muscles, cartilage, and so forth. Although natural healing potential of bone is sufficient to heal the common injuries, severe trauma and tumor-recession can abrogate germinal potential of bone-forming stem cells. In vitro chondrogenic, osteogenic, and adipogenic potential of MSCs advocates therapeutic applications of MSCs in orthopedic injuries [[53](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/" \l "B56)]. Seeding of MSCs, coaxed into biomaterial scaffolds, at defective bone tissue, regenerates defective bone tissues, within four wks of transplantation; by the end of 32 wks newly formed tissues integrate into old bone [[54](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/" \l "B57)]. Osteoblasts, the bone-forming cells, have lesser actin cytoskeleton compared to adipocytes and MSCs. Treatment of MSCs with cytochalasin-D causes rapid transportation of G-actin, leading to osteogenic transformation of MSCs. Furthermore, injection of cytochalasin-D to mice tibia also promotes bone formation within a wk time frame [[55](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/" \l "B58)]. The bone formation processes in mice, dog, and human are fundamentally similar, so outcomes of research on mice and dogs can be directional for regenerative application to human. Injection of MSCs to femur head of Legg-Calve-Perthes suffering dog heals the bone very fast and reduces the injury associated pain [[55](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/" \l "B58)]. Degeneration of skeletal muscle and muscle cramps are very common to sledge dogs, animals, and individuals involved in adventurous athletics activities. Direct injection of adipose tissue derived MSCs to tear-site of semitendinosus muscle in dogs heals injuries much faster than traditional therapies [[56](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/" \l "B59)]. Damage effect treatment for heart muscle regeneration is much more complex than regeneration of skeletal muscles, which needs high grade fine-tuned coordination of neurons with muscles. Coaxing of MSCs into alginate gel increases cell retention time that leads to releasing of tissue repairing factors in controlled manner. Transplantation of alginate encapsulated cells to mice heart reduces scar size and increases vascularisation, which leads to restoration of heart functions. Furthermore, transplanted MSCs face host inhospitable inflammatory immune responses and other mechanical forces at transplantation site, where encapsulation of cells keeps them away from all sorts of mechanical forces and enables sensing of host tissue microenvironment, and respond accordingly [[57](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/" \l "B60)]. Ageing, disease, and medicine consumption can cause hair loss, known as alopecia. Although alopecia has no life threatening effects, emotional catchments can lead to psychological disturbance. The available treatments for alopecia include hair transplantation and use of drugs, where drugs are expensive to afford and generation of new hair follicle is challenging. Dermal papillary cells (DPCs), the specialized MSCs localized in hair follicle, are responsible for morphogenesis of hair follicle and hair cycling. The layer-by-layer coating of DPCs, called GAG coating, consists of coating of geletin as outer layer, middle layer of fibroblast growth factor 2 (FGF2) loaded alginate, and innermost layer of geletin. GAG coating creates tissue microenvironment for DPCs that can sustain immunological and mechanical obstacles, supporting generation of hair follicle. Transplantation of GAG-coated DPCs leads to abundant hair growth and maturation of hair follicle, where GAG coating serves as ECM, enhancing intrinsic therapeutic potential of DPCs [[58](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/" \l "B61)]. During infection, the inflammatory cytokines secreted from host immune cells attract MSCs to the site of inflammation, which modulates inflammatory responses, representing MSCs as key candidate of regenerative medicine for infectious disease therapeutics. Coculture of macrophages (Mϕ) and adipose derived MSCs from Leishmania major (LM) susceptible and resistant mice demonstrates that AD-MSCs educate Mϕ against LM infection, differentially inducing M1 and M2 phenotype that represents AD-MSC as therapeutic agent for leishmanial therapy [[93](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512/" \l "B62)]. In summary, the multilineage differentiation potential of MSCs, as well as adoption of next-generation organoid culture system, avails MSCs as ideal regenerative medicine candidate. ------ Mahla RS (2016). ["Stem cells application in regenerative medicine and disease therapeutics"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512). *International Journal of Cell Biology*. 2016 (7): 19. [doi](https://en.wikipedia.org/wiki/Digital_object_identifier" \o "Digital object identifier):[10.1155/2016/6940283](https://doi.org/10.1155/2016/6940283). [PMC](https://en.wikipedia.org/wiki/PubMed_Central" \o "PubMed Central) [4969512](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969512) Freely accessible. [PMID](https://en.wikipedia.org/wiki/PubMed_Identifier" \o "PubMed Identifier) [27516776](https://www.ncbi.nlm.nih.gov/pubmed/27516776)

--Pattern formation

The introduction of this paper <http://www.mbl.edu/physiology/files/2014/06/Wolpert1969.pdf.>

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