We are IntechOpen, the world's leading publisher of Open Access books
Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 3

Adult Stem Cell Membrane Markers: Their Importance and Critical Role in Their Proliferation and Differentiation Potentials

Maria Teresa Gonzalez Garza

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.76869

Abstract

The stem cells are part of the cells that belong to the stromal tissue. These cells remain in a quiescent state until they are activated by different factors, usually those generated by an alteration in the parenchymal tissue. These cells have characteristic membrane markers such as CD73, CD90, and CD105. Those are a receptor, which in response to their ligand induces strong changes in different metabolic pathways that lead to these cells, both to generate molecules with different activities and to leave their stationary phase to reproduce and even differentiate. This review describes the metabolic pathways dependent on these membrane markers and how they influence on parenchymal tissue and other stromal cells.

Keywords: stromal cells, stem cells, membrane markers, CD73, CD90, CD

1. Introduction

Stromal cells make up some connective tissues for particular organs and give support by surrounding other tissues and organs. As result, stromal cells provide support, structure, and anchoring for many organs inside the body. The generic term "stromal cells" clearly the phenotypic and functional complexity of these cells. In addition, to their main functions in helping support organs and acting as connective tissues, stromal cells respond with metabolic adaptations to different inductions factors and play an important role in the microenvironment [1]. Stromal cells are able to react to physical and chemical signals of tissue damage. Physical stress such as mechanical stress activates channels (SACs) on the cell membrane [2].

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

On cells attached to an extracellular matrix, SACs initiate the remodeling of cell membrane structures called integrins. Membrane receptors rapidly send signals to the nucleus which initiate the synthesis of proteins, which in turn interact with cell metabolism and the surrounding environment to induce the modulation of recovery of parenchymal tissue function. Fibroblasts, pericytes, and stem cells are among the most common types of stromal cells. In this chapter, we analyze the membrane markers of stem cells and assess their capacity to influence surrounding tissues and recover tissue functionality.

2. How adult stem cell markers work?

Stem cells are composed of multiple types of cells, and all of them are characterized as undifferentiated cells able to self-renew and proliferate with high capacity. The international society for cellular therapy minimal criteria to define human MSC: (1) Mesenchymal stem cells (MSC) must be plastic adherent in standard culture conditions. (2) MSC must express CD105, CD73, and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR surface molecules. (3) MSC must differentiate to osteoblasts, adipocytes, and chondroblasts in vitro [3, 4]. Membrane markers are also present on other cells with high proliferation rates such as in the intestinal epithelium, ischemic myocardium, cholinergic synapses and in proliferative lymphocyte, and tumoral cells.

This review aims to analyze why those membrane markers are important to maintain important characteristics of stem cells such as proliferation potential, angiogenic, differentiation, and immunomodulation capacity. We assess how membrane markers promote the growth, proliferation, differentiation, and survival of parenchymal cells where stem cells reside. These cell membrane markers contribute under appropriate stimuli to the capacity of stem cells to differentiate into endoderm, mesoderm, or ectoderm-derived cell tissues.

2.1. CD73 membrane marker

CD73 participates in an autocrine and paracrine manner to the regulation of a variety of physiological processes. The primary structure of CD73 was described by Misumi et al. [5] as a dimer of two identical 70-kD subunits bound by a glycosylphosphatidylinositol linkage to the external face of the plasma membrane. This molecule is an ecto-5′-nucleotidase, which dephosphorylates nucleoside adenosine monophosphate (AMP) into adenosine (ADO). ADO is a potent endogenous physiological and pharmacological regulator of many functions. ADO mediates its effects on tissue regeneration and repair via binding and activation of a family of G protein-coupled receptors (adenosine A1, A2A, A2B, and A3 receptors). Activation of the G protein activates the PKA pathway by activating cyclic AMP. PKA is an enzyme that transfers a phosphate group from ATP to other specific proteins such as the cyclic AMP response element-binding protein (CREB). PKA is a transcriptional coactivator that stimulates the transcription of several genes by a phosphorylation pathway of kinases. Between those kinases, extracellular signal-regulated kinases (ERK) activate many transcription factors such as activating protein 1 (AP1). AP1 controls a number of cellular processes including differentiation, proliferation, and apoptosis [6–8]. Being one of the target genes of Cyclin D,

AP1 transcription factors are also associated with tissue regeneration. Cyclin D is a protein involved in regulating cell cycle progression by regulating the G1–to-S phases [9]. AP1 also induces CREB, another transcription factor responsible for increasing or decreasing the transcription of downstream genes [10]. The presence of CD73 in the cell membrane allows this enzyme to release ADO from extracellular AMP. ADO then binds to a membrane receptor associated with the G protein. Activation of the G protein induces a phosphorylation cascade that allows the activation of transcription factors. The target genes of these transcription factors are those involved with the cell cycle, the synthesis of extracellular matrix, and vascular growth factors (**Figure 1**). Nevertheless, activation of these receptors induces variable responses in different cells.

The pathway generates the liberation of extracellular ADO and could be responsible for the angiogenic effects observed in stem cell transplantation. Because of the dephosphorylate enzymatic activity of CD73 on AMP, the pathway induces the synthesis of VEGF. Indirectly, CD73 is responsible for the angiogenic capacity of stem cells as generating ADO by autocrine signaling will consequently stimulate the production of VEGF, a pro-angiogenic factor. For example, in skeletal muscle cells, activated PKA phosphorylates enzymes involved in glycogen metabolism which simultaneously trigger the breakdown of glycogen to glucose and inhibit glycogen synthesis, thereby increasing the amount of glucose available to muscle cells within seconds. In macrophages, it also induces the synthesis of angiogenic factors, such as VEGF and the proliferation of human retinal endothelial cells [11–13]. The pathway also plays an important role in the proliferation of endothelial cells. Stimulation of A2A receptors could be responsible for wound healing by stimulating both angiogenesis and matrix production [14]. Montesinos et al. [15] proposed that ADOA2A receptor stimulation by ADO promotes the recruitment of circulating bone marrow-derived endothelial precursor cells and differentiation into endothelial cells. CD73 serves as a costimulatory molecule in activating T cells [16].

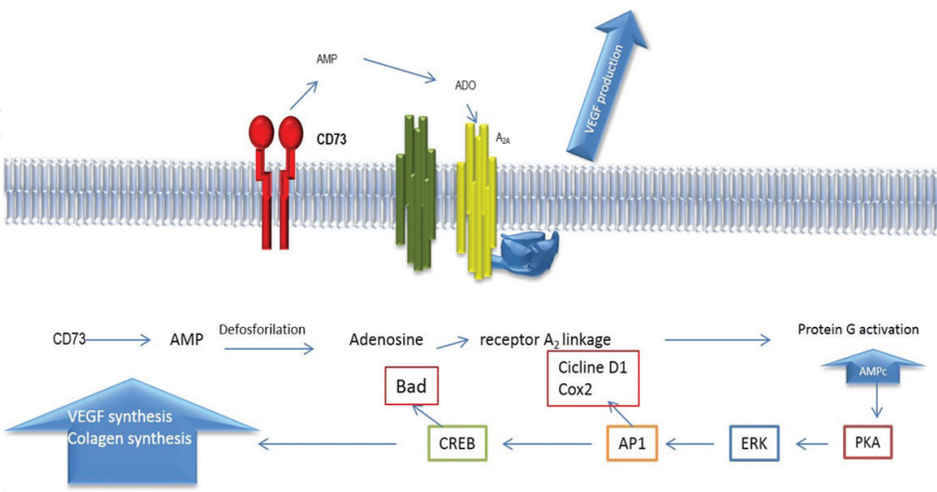

Figure 1. Schematic CD73 signaling pathways. The activity of ectonuclease on extra-cytoplasmic AMP releases (ADO). ADO binds to its receptor which in turn generates the activation of the G protein and triggers the phosphorylation cascade up to transcription factors that will induce the expression of genes responsible for the synthesis of collagen and vascular endothelial growth factors (VEGF).

Several activities for CD73 and its product ADO have been described, including interactions of ADO with its receptor in hematopoietic cells given the activation and angiogenic capabilities of those cells. Probably, in stem cells, the CD73 transmembrane protein is related to the capacity of cells to differentiate into several lineages because the A2A receptor has been inoculated as a possible regulator of osteoblast differentiation in bone tissues [17]. The pathway generated by this membrane marker induces the synthesis of extracellular matrix and promotes collagen production in the skin and in the liver [18–20].

Another activity observed in stem cells is their immunomodulatory potential, which is related to ADO inhibition against inflammatory actions by neutrophils [21]. ADO is also a neuromodulator acting through A1 and A2 receptors. A1Rs are abundantly expressed throughout the brain and control synaptic transmission. Because of its participation in cAMP formation in synaptosomes, CD73 has been proposed as an alternative target in the treatment of some cases of synaptic degeneration and neurodegeneration [22, 23].

CD73 has been related with cardiopathies as ADO produced by the 5′-nucleotidase activity of CD73 could exert control over the mineralization of the aortic valve [24]. Development and maturation of arterial atherosclerotic plaques have been related to the impaired expression of CD73. The production of ADO by CD73 is critical for adaptation to hypoxia in the myocardium, where CD73-catalyzed ADO production acts as a critical control point for the maintenance and regulation of vascular barrier function in multiple tissues under hypoxia [25, 26].

Other stromal cells bearing CD73 are fibroblasts, which are the most common cells in connective tissues. Fibroblasts synthesize the extracellular matrix that includes collagen, glycosaminoglycans, elastic fibers, and glycoproteins, as well as participate in inflammatory responses. Fibroblasts aid to maintain the structural integrity of connective tissues [27–29]. On those activities are involved with the CD73 membrane marker that allows the activation of the G-protein followed by a pathway to induce the activation of the transcription factors responsible for the synthesis of extracellular matrix molecules.

2.2. CD90 membrane marker

Early studies on THY1 and CD90 have suggested their possible relation with cell activation in progenitor's cells with the highest in vitro proliferative potential [30]. THY1 is signaled via integrins, protein tyrosine kinases, cytokines, and growth factors. Several functions have been related to THY1 such as T-cell activation, neurite outgrowth, apoptosis, tumor suppression, wound healing, and fibrosis [31–34]. In order to understand how this membrane receptor induces so many changes in cellular metabolism, numerous studies have been conducted to identify possible activation pathways induced by the activation of THY1. THY1 is a glycophosphatidylinositol (GPI) anchored to conserved cell surface protein with a single V-like immunoglobulin domain. The protein is anchored in the external lipid bilayer of the membrane by a phosphatidylinositol (PI) anchor in membrane microdomains (lipid rafts) [35, 36].

Studies focusing on understanding why this membrane protein induces several changes in cellular pathways have reported that THY1 stimulates neurite outgrowth by activating a second messenger pathway where extracellular signals such as growth factors. Its activation induces a rapid and extensive mobilization of the intracellular second messengers, PI, and

Ca^{2+} [37]. T-cell activation by THY1 causes an immediate phosphatidylinositol (PI) turnover and an influx of extracellular Ca^{2} while releasing very little Ca^{2+} from intracellular stores [38]. Intracellular transduction of the G protein activates phospholipase C that generates inositol phosphate and diacylglycerol (a second messenger) groups from the hydrolysis of plasma membrane phospholipids. Inositol phosphate could be phosphorylated at various positions by enzymes that belong to the family of phosphatidylinositol 5-phosphate 4-kinases. The resulted PI is a second messenger involved in several signaling pathways including signals of cell growth [39–42]. IP3 releases Ca^{2+} from the endoplasmic reticulum by binding to its receptors (IP3R) regulating mitochondrial metabolism, cell cycle entry, and cell survival. Ca^{2+} signals are important for the self-renewal and differentiation of human embryonic stem cells [43–45]. Ca^{2+} forms a complex with the protein calmodulin which regulates the activity of many proteins including various transcription factors [46, 47]. Diacylglycerol is a glyceride of two fatty acid chains covalently bonded to a glycerol molecule through ester linkages and it remains within the plasma membrane where it regulates the protein kinase signaling cascades through protein kinase C (PKC) activation [48].

High capacity for cell proliferation is induced via CDk5 and ERK, generating changes in the cytoskeleton that induce cell proliferation and differentiation, matrix production and immunomodulatory potential. Recently, Chung et al. [49] demonstrated that a subpopulation that is positive for THY1 (CD90) is relatively more capable of forming bone than the CD105 low subset of cells. Considering the possible differentiation and proliferation capacity of cells carrying this membrane protein, stromal cardiac cells with the CD90 antigen were introduced to recover function, and reprogramming capacities in an infarcted heart. Cells obtained from human bone marrow-bearing this membrane marker exhibited robust multi-lineage differentiation and self-renewal potency. In addition, THY1 expression appears to be an indicator of G_0/G_1cell-cycle phase in human stem cells from bone marrow [50–53]. THY1 has possible roles in cell–cell interaction where THY1 mediates adhesion of leukocytes and monocytes to endothelial cells and fibroblasts and performs a signaling event, which results in the activation of cell pathways.

THY1 is a receptor to many molecules such as growth factors, hormones, and the extracellular matrix. Its stimulation induces the synthesis of second messengers that initiate a cascade of reactions that can lead to the cell to proliferation or differentiation (**Figure 2**).

In fibroblasts expressing the endometrial stromal marker CD90 (THY1) [54], CD90 was strongly expressed by functional stroma and perivascular cells and used to isolate pure populations of endometrial stromal stem and progenitor cells [55]. In fibroblasts, these membrane markers are stimulated by peptide growth factors, such as bombesin and PDGF, thereby inducing DNA synthesis and cell division. In addition, since apoptosis is a mechanism during normal wound healing, THY1 has a beneficial effect on lung fibroblast activity where it induces the regulation of apoptosis via Fas-, Bcl-, and caspase-dependent pathways [56].

2.3. CD105 membrane marker

Endoglin, a cell membrane glycoprotein also known as CD105, is over-expressed in proliferating endothelial cells and as consequence is involved in neovascularization. It is a

transmembrane glycoprotein related to the transforming growth factor (TGF)-β receptor. St-Jaques et al. [57] suggested that endoglin on stromal fibroblast-like cells may be regulating the access of TGF-β1 to the signaling receptor complex. It was later confirmed that CD105 is a transmembrane protein that binds to several factors of the TGF-β superfamily, a pleiotropic cytokine that regulates different cellular functions including proliferation, differentiation, and migration [58]. Endoglin binds TGF-β1 and TGF-β3 with high affinity through its association with the TGF-β receptor type II [59]. After TGF-β binding to its receptor via two single pass serine/threonine kinase transmembrane proteins, a phosphorylate kinase activates signaling cascade transduction, which initiates intracellular signaling by phosphorylating members of the Smad family of transcription. The resulting Smad heterocomplex translocates into the nucleus and interacts with numerous transcription factors that in turn regulate the transcription of many TGF-β-responsive genes [60, 61]. Upon ligand stimulation, R-Smads are phosphorylated by receptors and form oligomeric complexes with common-partner Smads (Co-Smads). Oligomeric Smad complexes then translocate into the nucleus where they regulate the transcription of target genes by direct binding to DNA. CD105 co-stimulates the TGF-β receptor to induce CDk5 and other genes by the Smad4 pathway leading to high cell proliferation and collagen production (**Figure 3**).

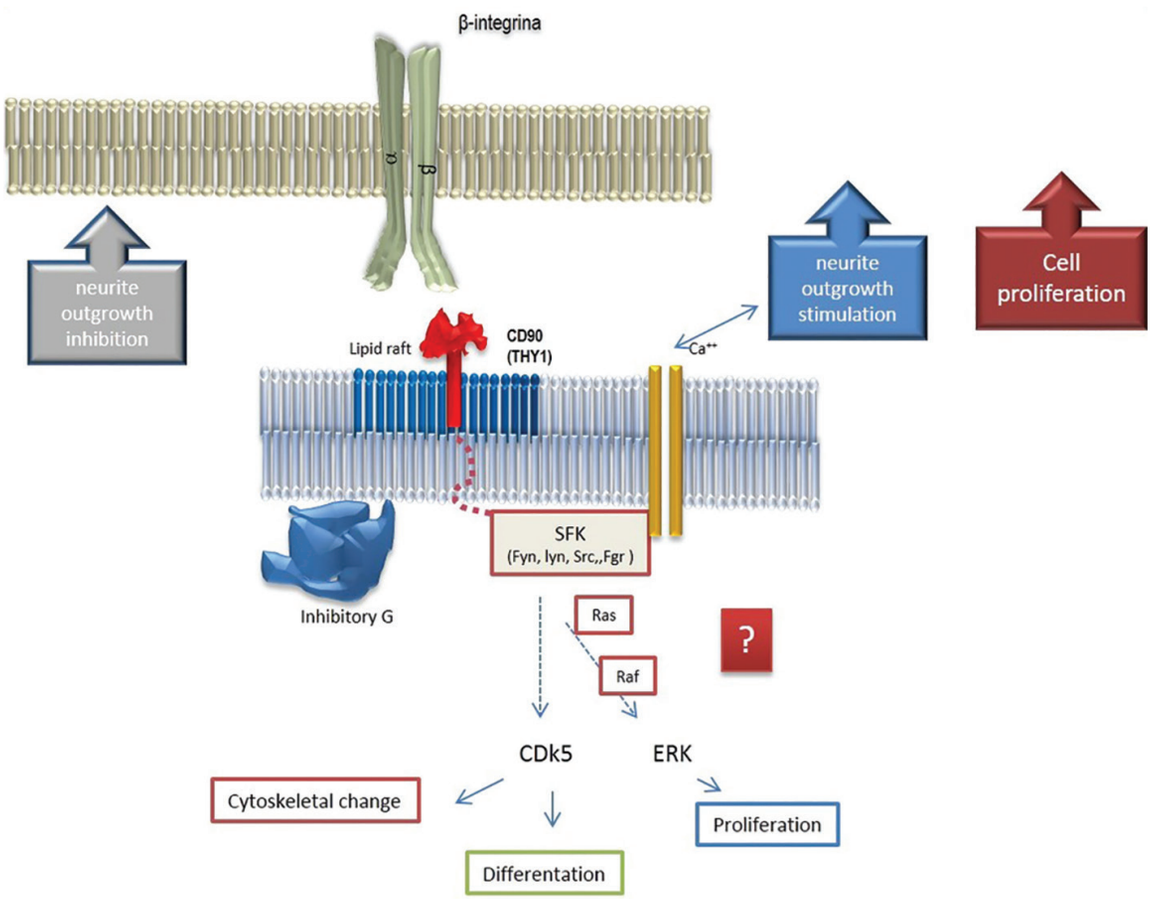

Figure 2. Schematic representation of CD90 pathway induction. GPI is anchored in the cell membrane surface and its activation generates an efflux of calcium and a release of phosphatidylinositol (PI). These second messengers regulate mitochondrial metabolism, cell cycle entry, and cell survival.

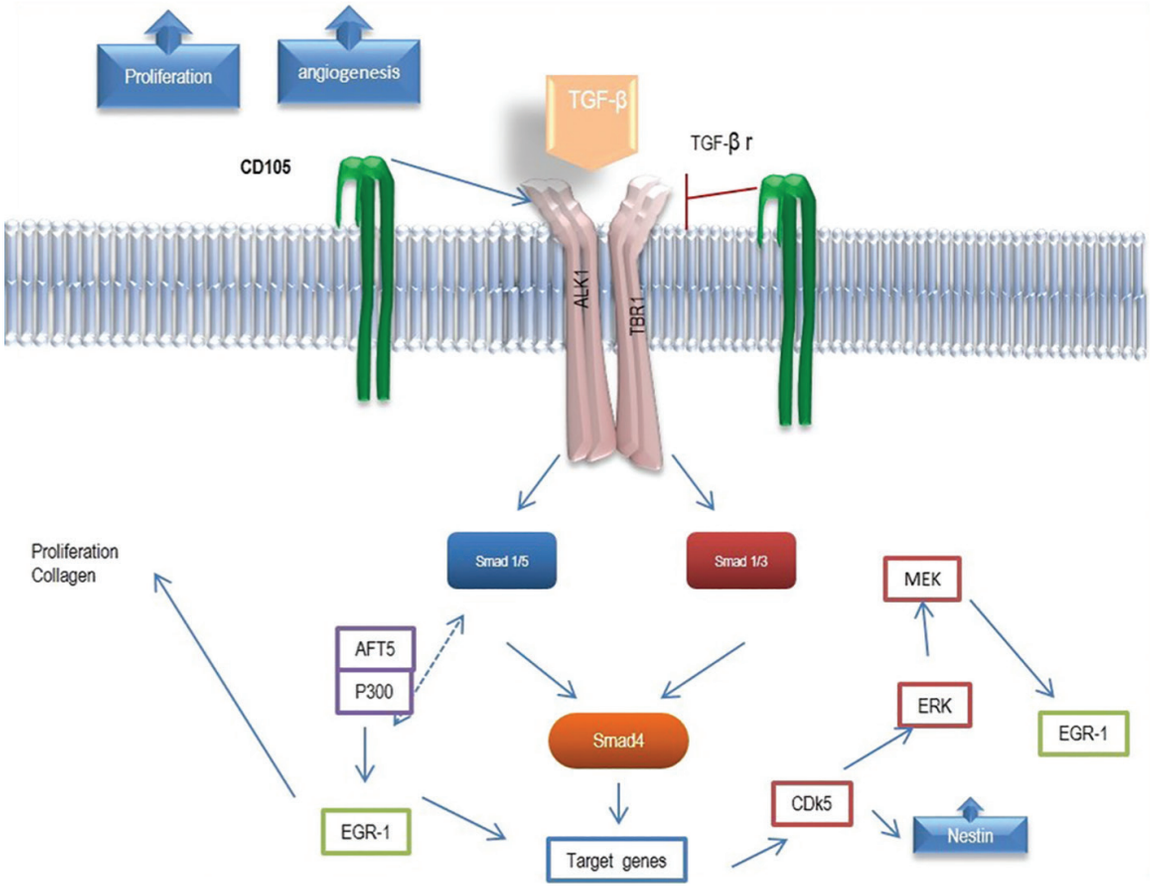

Figure 3. Schematic representation of CD105 pathways. The membrane protein binds to the transforming growth factor receptor (TGFr). Following TGF binding with its receptor, a signaling cascade leads the transcription of different genes related to cell differentiation, chemotaxis, proliferation, and activation across many cells.

The biological functions of TGF-β can only be delivered after ligand activation and they promote or inhibit cell proliferation. The activation of TGF-β is involved in the recruitment of stem and progenitor cell participation in the tissue regeneration and remodeling process [62, 63].

In some cases, the expression of endoglin has been related to its differentiation selectivity. Levi et al. [64] found that a subset of adipose-derived stem cells with low expression of the endoglin cell surface receptor (CD105) had enhanced in vitro and in vivo osteogenic differentiation potential. Nevertheless, more recent research in an osteoarthritis animal model has reported that $CD105^{+}$-MSCs migrated toward the injured knee joint and suggested the use of $CD105^{+}$-MSC as an alternative for cell therapy for these pathologies [65, 66]. Because CD105 is a co-factor component of the TGF-β receptor complex that is expressed in endothelial cells, it has been related to the pathogenesis of vascular diseases and with tumor progression [67, 68]. Nevertheless, TGF-β has been shown to activate two distinct pathways, ALK5-inducing Smad2/3 phosphorylation, and ALK1-promoting Smad1/5 phosphorylation. Those pathways regulate endothelial cell proliferation. Activation of ALK1 stimulates cell proliferation and migration, whereas activation of ALK5 inhibits these responses [69, 70]. Cell therapy may reconstitute the entire hematopoietic system with cells bearing CD105. Since TGF-β1 exerts its action on primitive hematopoiesis by inhibiting cell cycle progression of primitive precursors,

a previous report has shown that the presence of cells bearing CD34 represents an option to recover hematopoietic stem cells. Recently, it has been reported that human stem cells bearing CD34 and CD105 are the best long-term repopulating cells and present high self-renewal capacities [71, 72]. Nevertheless, balance is very important and these cells have been related to pathologies such as fibrosis diseases [73, 74].

3. Conclusions

The membrane markers CD73, CD90, and CD105 allow stem cells and other stromal cells such as fibroblasts to react to stimuli and quickly leave their quiescent state, thereby going into a proliferation state and generating growth factors. Those capacities allow the recovery of parenchymal tissue in which they are found. CD73 is an ectoenzyme that dephosphorylates nucleoside AMP given free ADO. This purine binding to its membrane receptor leads to the activation of the G protein and results in the activation of a pathway that reaches the nucleus. As a consequence, extracellular matrix and growth factors such as VEGF are synthesized. CD90 influences the cell cycle and cell proliferation. CD90 also induce several cytoskeletal changes allowing cell differentiation. CD105 is a co-factor to the TGF-β receptor and following TGF-β union with its receptor a signaling cascade is activated, resulting in the transcription of different effectors including the synthesis of pro-inflammatory cytokines, which have an important role in angiogenesis and proliferation. In conclusion, those membrane markers are related to pathways that regulate the immune response, cell proliferation, and differentiation, thereby allowing lost tissue recovery and the formation of new angiogenic pathways.

Acknowledgements

This work was partially funded by endowments from Instituto Tecnológico de Estudios Superiores de Monterrey (cat-134) and the Zambrano–Hellion Foundation.

Conflict of interest

The author declares have no competing interests.

Author details

Maria Teresa Gonzalez Garza

Address all correspondence to: mtgonzalezgarza@itesm.mx

Tecnologico de Monterrey, Escuela Nacional de Medicina Monterrey, NL, Mexico

References

[1] Ghesquière B, Wong BW, Kuchnio A, Carmeliet P. Metabolism of stromal and immune cells in health and disease. Nature. 2014;**511**(7508):167-176

[2] Shah N, Morsi Y, Manasseh R. From mechanical stimulation to biological pathways in the regulation of stem cell fate. Cell Biochemistry and Function. 2014;**32**(4):309-325

[3] Horwitz EM, Le Blanc K, Dominici M, Mueller I, Slaper-Cortenbach I, Marini FC, Deans RJ, Krause DS, Keating A. International society for cellular therapy. Clarification of the nomenclature for MSC: The international society for cellular therapy position statement. Cytotherapy. 2005;**7**(5):393-395

[4] Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Dj P, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The international society for cellular therapy position statement. Cytotherapy. 2006;**8**(4):315-317

[5] Misumi Y, Ogata S, Ohkubo K, Hirose S, Ikehara Y. Primary structure of human placental 5′-nucleotidase and identification of the glycolipid anchor in the mature form. European Journal of Biochemistry. 1990;**191**(3):563-569

[6] Shaulian E, Karin M. AP-1 as a regulator of cell life and death. Nature Cell Biology. 2002;**4**(5):E131-E136

[7] Ameyar M, Wisniewska M, Weitzman JB. A role for AP-1 in apoptosis: The case for and against. Biochimie. 2003;**85**(8):747-752

[8] Subramanian D, Bunjobpol W, Sabapathy K. Interplay between TAp73 protein and selected activator protein-1 (AP-1) family members promotes AP-1 target gene activation and cellular growth. The Journal of Biological Chemistry. 2015;**290**(30):18636-18649

[9] Resnitzky D, Reed SI. Different roles for cyclins D1 and E in regulation of the G1-to-S transition. Molecular and Cellular Biology. 1995;**15**(7):3463-3469

[10] Bourtchuladze R, Frenguelli B, Blendy J, Cioffi D, Schutz G, Silva AJ. Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein. Cell. 1994, Oct 7;**79**(1):59-68

[11] Grant MB, Tarnuzzer RW, Caballero S, Ozeck MJ, Davis MI, Spoerri PE, Feoktistov I, Biaggioni I, Shryock JC, Belardinelli L. Adenosine receptor activation induces vascular endothelial growth factor in human retinal endothelial cells. Circulation Research. 1999;**85**(8):699-706

[12] Pinhal-Enfield G, Ramanathan M, Hasko G, Vogel SN, Salzman AL, Boons GJ, Leibovich SJ. An angiogenic switch in macrophages involving synergy between toll-like receptors 2, 4, 7, and 9 and adenosine A(2A) receptors. The American Journal of Pathology. 2003;**163**:711-721

[13] Leibovich SJ, Chen JF, Pinhal-Enfield G, Belem PC, Elson G, Rosania A, Ramanathan M, Montesinos C, Jacobson M, Schwarzschild MA, Fink JS, Cronstein B. Synergistic up-regulation of vascular endothelial growth factor expression in murine macrophages by adenosine A(2A) receptor agonists and endotoxin. The American Journal of Pathology. 2002;**160**(6):2231-2244

[14] Cronstein BN. Adenosine receptors and fibrosis: A translational review. F1000 Biology Reports. 2011;**3**:21. DOI: 10.3410/B3-21

[15] Montesinos MC, Shaw JP, Yee H, Shamamian P, Cronstein BN. Adenosine A(2A) receptor activation promotes wound neovascularization by stimulating angiogenesis and vasculogenesis. The American Journal of Pathology. 2004;**164**:1887-1892

[16] Resta R, Thompson LF. T cell signalling through CD73. Cellular Signalling. 1997;**9**(2): 131-139

[17] Takedachi M, Oohara H, Smith BJ, Iyama M, Kobashi M, Maeda K, Long CL, Humphrey MB, Stoecker BJ, Toyosawa S, Thompson LF, Murakami S. CD73-generated adenosine promotes osteoblast differentiation. Journal of Cellular Physiology. 2012;**227**(6):2622-2631

[18] Chan ES, Liu H, Fernandez P, Luna A, Perez-Aso M, Bujor AM, Trojanowska M, Cronstein BN. Adenosine A(2A) receptors promote collagen production by a Fli1-and CTGF-mediated mechanism. Arthritis Research & Therapy. 2013;**15**(3):R58

[19] Shaikh G, Cronstein B. Signaling pathways involving adenosine A2A and A2B receptors in wound healing and fibrosis. Purinergic Signal. 2016;**12**(2):191-917

[20] Peng Z, Fernandez P, Wilder T, Yee H, Chiriboga L, Chan ES, Cronstein BN. Ecto-5′-nucleotidase (CD73)-mediated extracellular adenosine production plays a critical role in hepatic fibrosis. The FASEB Journal. 2008;**22**:2263-2272

[21] Haskó G, Cronstein B. Regulation of inflammation by adenosine. Frontiers in Immunology. 2013;**4**:85. DOI: 10.3389/fimmu.2013.00085

[22] Dunwiddie TV, Masino SA. The role and regulation of adenosine in the central nervous system. Annual Review of Neuroscience. 2001;**24**:31-55

[23] Augusto E, Matos M, Sévigny J, El-Tayeb A, Bynoe MS, Müller CE, Cunha RA, Chen JF. Ecto-5′-nucleotidase (CD73)-mediated formation of adenosine is critical for the striatal adenosine A2A receptor functions. The Journal of Neuroscience. 2013;**33**(28):11390-11399

[24] Mahmut A, Boulanger MC, Bouchareb R, Hadji F, Mathieu P. Adenosine derived from ecto-nucleotidases in calcific aortic valve disease promotes mineralization through A2A adenosine receptor. Cardiovascular Research. 2015;**106**(1):109-120

[25] Linden J. Molecular approach to adenosine receptors: Receptor-mediated mechanisms of tissue protection. Annual Review of Pharmacology and Toxicology. 2001;**41**:775-787

[26] Thompson LF, Eltzschig HK, Ibla JC, Van De Wiele CJ, Resta R, Morote-Garcia JC, Colgan SP. Crucial role for ecto-5′-nucleotidase (CD73) in vascular leakage during hypoxia. The Journal of Experimental Medicine. 2004;**200**(11):1395-1405

[27] Hogaboam CM, Steinhauser ML, Chensue SW, Kunkel SL. Novel roles for chemokines and fibroblasts in interstitial fibrosis. Kidney International. 1998;**54**(6):2152-21529

[28] Bonnans C, Chou J, Werb Z. Remodelling the extracellular matrix in development and disease. Nature Reviews. Molecular Cell Biology. 2014;**15**(12):786-801

[29] Lupatov AY, Vdovin AS, Vakhrushev IV, Poltavtseva RA, Yarygin KN. Comparative analysis of the expression of surface markers on fibroblasts and fibroblast-like cells isolated from different human tissues. Bulletin of Experimental Biology and Medicine. 2015;**158**(4):537-543

[30] Mayani H, Lansdorp PM. Thy-1 expression is linked to functional properties of primitive hematopoietic progenitor cells from human umbilical cord blood. Blood. 1994;**83**(9):2410-2417

[31] Hagood JS, Lasky JA, Nesbitt JE, Segarini P. Differential expression, surface binding, and response to connective tissue growth factor in lung fibroblast subpopulations. Chest. 2001;**120**(1 Suppl):64S-66S

[32] Barker TH, Grenett HE, MacEwen MW, Tilden SG, Fuller GM, Settleman J, Woods A, Murphy-Ullrich J, Hagood JS. Thy-1 regulates fibroblast focal adhesions, cytoskeletal organization and migration through modulation of p190 RhoGAP and Rho GTPase activity. Experimental Cell Research. 2004;**295**(2):488-496

[33] Rege TA, Hagood JS. Thy-1 as a regulator of cell-cell and cell-matrix interactions in axon regeneration, apoptosis, adhesion, migration, cancer, and fibrosis. The FASEB Journal. 2006;**20**(8):1045-1054

[34] Fiore VF, Strane PW, Bryksin AV, White ES, Hagood JS, Barker TH. Conformational coupling of integrin and Thy-1 regulates Fyn priming and fibroblast mechanotransduction. The Journal of Cell Biology. 2015;**211**(1):173-190. DOI: 10.1083/jcb.201505007. PubMed PMID: 26459603

[35] Craig W, Kay R, Cutler RL, Lansdorp PM. Expression of Thy-1 on human hematopoietic progenitor cells. The Journal of Experimental Medicine. 1993;**177**(5):1331-1342

[36] Williams AF. Immunology, neurology, and therapeutic applications. In: Reif AF, Schlesinger M, editors. Cell Surface Thy-1. New York: Marcel Dekker, Inc.; 1989. pp. 49-70

[37] Doherty P, Singh A, Rimon G, Bolsover SR, Walsh FS. Thy-1 antibody-triggered neurite outgrowth requires an influx of calcium into neurons via N- and L-type calcium channels. The Journal of Cell Biology. 1993;**122**(1):181-189

[38] Barboni E, Gormley AM, Pliego Rivero FB, Vidal M, Morris RJ. Activation of T lymphocytes by cross-linking of glycophospholipid-anchored Thy-1 mobilizes separate pools of intracellular second messengers to those induced by the antigen-receptor/CD3 complex. Immunology. 1991;**72**:457-463

[39] Toker A, Cantley LC. Signalling through the lipid products of phosphoinositide-3-OH kinase. Nature. 1997;**387**(6634):673-676

[40] Carpenter CL, Cantley LC. Phosphoinositide 3-kinase and the regulation of cell growth. Biochimica et Biophysica Acta. 1996;**1288**(1):M11-M16

[41] Bulley SJ, Clarke JH, Droubi A, Giudici ML, Irvine RF. Exploring phosphatidylinositol 5-phosphate 4-kinase function. Advances in Biological Regulation. 2015;**57**:193-202

[42] Roberts HF, Clarke JH, Letcher AJ, Irvine RF. Effect of lipid kinase expression and cellular stimuli on phosphatidylinositol 5-phosphate levels in mammalin cell lines. FEBS Letters. 2005;**579**:2868e72

[43] Berridge MJ, Bootman MD, Roderick HL. Calcium signalling: Dynamics, homeostasis and remodelling. Nature Reviews. Molecular Cell Biology. 2003;**4**(7):517-529

[44] Yanagida E, Shoji S, Hirayama Y, Yoshikawa F, Otsu K, Uematsu H, Hiraoka M, Furuichi T, Kawano S. Functional expression of Ca^{2+} signaling pathways in mouse embryonic stem cells. Cell Calcium. 2004;**36**(2):135-146

[45] Huang CY, Lien CC, Cheng CF, Yen TY, Chen CJ, Tsaur ML. K(+) channel Kv3.4 is essential for axon growth by limiting the influx of Ca(2+) into growth cones. The Journal of Neuroscience. 2017;**37**(17):4433-4449

[46] Stevens FC. Calmodulin: An introduction. Canadian Journal of Biochemistry and Cell Biology. 1983 Aug;**61**(8):906-910

[47] Chin D, Means AR. Calmodulin: A prototypical calcium sensor. Trends in Cell Biology. 2000;**10**(8):322-328

[48] Smrcka AV. Regulation of phosphatidylinositol-specific phospholipase C at the nuclear envelope in cardiac myocytes. Journal of Cardiovascular Pharmacology. 2015;**65**(3): 203-210

[49] Chung MT, Liu C, Hyun JS, Lo DD, Montoro DT, Hasegawa M, Li S, Sorkin M, Rennert R, Keeney M, Yang F, Quarto N, Longaker MT, Wan DC. CD90 (Thy-1)-positive selection enhances osteogenic capacity of human adipose-derived stromal cells. Tissue Engineering. Part A. 2013;**19**(7-8):989-997

[50] Takeda H, Yamamoto M, Morita N, Tanizawa T. Relationship between Thy-1 expression and cell-cycle distribution in human bone marrow hematopoietic progenitors. American Journal of Hematology. 2005;**79**(3):187-193

[51] Kawamoto K, Konno M, Nagano H, Nishikawa S, Tomimaru Y, Akita H, Hama N, Wada H, Kobayashi S, Eguchi H, Tanemura M, Ito T, Doki Y, Mori M, Ishii H. CD90-(Thy-1-) high selection enhances reprogramming capacity of murine adipose-derived mesenchymal stem cells. Disease Markers. 2013;**35**(5):573-579

[52] Mabuchi Y, Morikawa S, Harada S, Niibe K, Suzuki S, Renault-Mihara F, Houlihan DD, Akazawa C, Okano H, Matsuzaki Y. LNGFR(+)THY-1(+)VCAM-1(hi+) cells reveal functionally distinct subpopulations in mesenchymal stem cells. Stem Cell Reports. 2013;**1**(2):152-165

[53] Shen Y, Sherman JW, Chen X, Wang R. Phosphorylation of Cdc25C by AMP-activated protein kinase mediates a metabolic checkpoint during cell cycle G2/M phase transition. The Journal of Biological Chemistry. 2018:jbc.RA117.001379. DOI: 10.1074/jbc.RA117.001379

[54] Gargett CE. Identification and characterisation of human endometrial stem/progenitor cells. The Australian & New Zealand Journal of Obstetrics & Gynaecology. 2006;**46**(3):250-253

[55] Schwab KE, Hutchinson P, Gargett CE. Identification of surface markers for prospective isolation of human endometrial stromal colony-forming cells. Human Reproduction. 2008;**23**(4):934-943

[56] Liu X, Wong SS, Taype CA, Kim J, Shentu TP, Espinoza CR, Finley JC, Bradley JE, Head BP, Patel HH, Mah EJ, Hagood JS. Thy-1 interaction with Fas in lipid rafts regulates fibroblast apoptosis and lung injury resolution. Laboratory Investigation. 2017;**97**(3):256-267

[57] St-Jacques S, Cymerman U, Pece N, Letarte M. Molecular characterization and in situ localization of murine endoglin reveal that it is a transforming growth factor-beta binding protein of endothelial and stromal cells. Endocrinology. 1994;**134**:2645-2657

[58] Derynck R, Feng XH. TGF-b receptor signaling. Biochimica et Biophysica Acta. 1997;**1333**: F105-F150

[59] Barbara NP, Wrana JL, Letarte M. Endoglin is an accessory protein that interacts with the signaling receptor complex of multiple members of the transforming growth factor-b superfamily. The Journal of Biological Chemistry. 1999;**274**:584-594

[60] Miyazono K, ten Dijke P, Heldin CH. TGF-beta signaling by Smad proteins. Advances in Immunology. 2000;**75**:115-157

[61] Schiller M, Javelaud D, Mauviel A. TGF-beta-induced SMAD signaling and gene regulation: Consequences for extracellular matrix remodeling and wound healing. Journal of Dermatological Science. 2004;**35**(2):83-92

[62] Verrecchia F, Mauviel A. Transforming growth factor-beta signaling through the Smad pathway: Role in extracellular matrix gene expression and regulation. The Journal of Investigative Dermatology. 2002;**118**(2):211-215

[63] Xu L, Liu Y, Hou Y, Wang K, Wong Y, Lin S, Li G. U0126 promotes osteogenesis of rat bone-marrow-derived mesenchymal stem cells by activating BMP/Smad signaling pathway. Cell and Tissue Research. 2015;**359**(2):537-545

[64] Levi B, Wan DC, Glotzbach JP, Hyun J, Januszyk M, Montoro D, Sorkin M, James AW, Nelson ER, Li S, Quarto N, Lee M, Gurtner GC, Longaker MT. CD105 protein depletion enhances human adipose-derived stromal cell osteogenesis through reduction of transforming growth factor beta1 (TGF-beta1) signaling. The Journal of Biological Chemistry. 2011;**286**:39497-39509

[65] Arufe MC, De la Fuente A, Fuentes-Boquete I, De Toro FJ, Blanco FJ. Differentiation of synovial CD-105(+) human mesenchymal stem cells into chondrocyte-like cells through spheroid formation. Journal of Cellular Biochemistry. 2009;**108**(1):145-155

[66] Fernandez-Pernas P, Rodríguez-Lesende I, de la Fuente A, Mateos J, Fuentes I, De Toro J, Blanco FJ, Arufe MC. CD105+-mesenchymal stem cells migrate into osteoarthritis joint: An animal model. PLoS One. 2017;**12**(11):e0188072. DOI: 10.1371/journal.pone.0188072

[67] Fonsatti E, Sigalotti L, Arslan P, Altomonte M, Maio M. Emerging role of endoglin (CD105) as a marker of angiogenesis with clinical potential in human malignancies. Current Cancer Drug Targets. 2003;**3**(6):427-432

[68] Dallas NA, Samuel S, Xia L, Fan F, Gray MJ, Lim SJ, Ellis LM. Endoglin (CD105): A marker of tumor vasculature and potential target for therapy. Clinical Cancer Research. 2008;**14**(7):1931-1937

[69] Goumans MJ, Valdimarsdottir G, Itoh S, Rosendahl A, Sideras P, ten Dijke P. Balancing the activation state of the endothelium via two distinct TGF-beta type I receptors. The EMBO Journal. 2002;**21**(7):1743-1753

[70] Lebrin F, Goumans MJ, Jonker L, Carvalho RL, Valdimarsdottir G, Thorikay M, Mummery C, Arthur HM, ten Dijke P. Endoglin promotes endothelial cell proliferation and TGF-beta/ALK1 signal transduction. The EMBO Journal. 2004;**23**(20):4018-4028

[71] Hatzfeld J, Li ML, Brown EL, Sookdeo H, Levesque JP, ÓToole T, Gurney C, Clark SC, Hatzfeld A. Release of early human hematopoietic progenitors from quiescence by antisense transforming growth factor beta 1 or Rb oligonucleotides. The Journal of Experimental Medicine. 1991;**174**:925-929

[72] Kays SK, Kaufmann KB, Abel T, Brendel C, Bonig H, Grez M, Buchholz CJ, Kneissl S. CD105 is a surface marker for receptor-targeted gene transfer into human long-term repopulating hematopoietic stem cells. Stem Cells and Development. 2015;**24**(6):714-723

[73] Wynn TA, Ramalingam TR. Mechanisms of fibrosis: Therapeutic translation for fibrotic disease. Nature Medicine. 2012;**18**(7):1028-1040

[74] Pardali E, Sanchez-Duffhues G, Gomez-Puerto MC, Ten Dijke P. TGF-β-induced endothelial-mesenchymal transition in fibrotic diseases. International Journal of Molecular Sciences. 2017;**18**(10):E2157. DOI: 10.3390/ijms18102157