ISSN (Online) 2287-3406
Journal of Life Science **2021** Vol. 31. No. 9. 856~861 DOI : https://doi.org/10.5352/JLS.2021.31.9.856

- Review -

Beyond the Molecular Facilitator, CD82: Roles in Metastasis Suppressor, Stem Cell Niche, Muscle Regeneration, and Angiogenesis

Hyun-Chae Lee[1], Jung-Hwa Han[1,2] and Jin Hur[1,2]*

[1]*Department of Convergence Medicine, Pusan National University School of Medicine, Yangsan 50612, Korea*
[2]*PNU GRAND Convergence Medical Science Education Research Center, Pusan National University School of Medicine, Yangsan 50612, Korea*

Received August 20, 2021 /Revised September 16, 2021 /Accepted September 23, 2021

CD82/KAI1, identified as a metastasis suppressor, was initially known only as a molecular facilitator, but its various functions have recently been revealed. CD82 plays an important role in the stem-progenitor cell, angiogenesis, and muscle. We would like to introduce the recently reported functions and roles of CD82 in this review. CD82 is a member of the tetraspanin family, which consists of four transmembrane domains. The interaction between CD82 and cell adhesion molecules suppresses the metastasis of cancer. CD82 regulates the cell cycle of stem-progenitor cells in the stem cell niche. In the bone marrow, CD82 is expressed on long-term repopulating hematopoietic stem cells (LT-HSCs), which show multipotent differentiation potential. The interaction between CD82 and Duffy antigen receptor for chemokines (DARC) induces quiescence in LT-HSCs. CD82 also regulates Rac1 activity, resulting in the homing and engraftment of HSCs into the bone marrow niche. Besides, CD82 maintains the differentiation potential of muscle stem cells and prevents angiogenesis by inhibiting the expression of cytokines, such as IL-6 and VEGF and adhesion molecules in endothelial cells. CD82 is a key membrane protein that distinguishes the hierarchy of stem-progenitor cells, and is also important for amplification and verification of cellular resources. Further studies on the function of CD82 in various organs and cells are expected to advance cell biology and cell therapy.

Key words : Angiogenesis, CD82/KAI1, metastasis suppressor, muscle satellite cell, stem cell niche

Introduction

As the name suggests, tetraspanin is a transmembrane and a scaffold protein with a structure that passes through the cell membrane four times [11]. It is a molecular facilitator that promotes functions by interacting with adjacent proteins [42]. There are 34 types of tetraspanins in mammals, widely expressed in various types of tissues, blood cells, and cancer cells, and play various roles in cell migration, adhesion, morphology, invasion, and signal transduction [11]. CD82, also called C33, R2, 4F9, and IA4, is a type of tetraspanin and was initially involved in the T-cell activation process [17, 38]. Most of the CD82 research has been limited to its role as a metastasis suppressor in cancer, but recently its role in cells of various tissues, such as bone marrow, blood, blood vessels, muscle, and heart, has been revealed, sequentially [2, 11]. Recent studies have shown the various functions of CD82, including the maintenance of dormancy of long-term repopulating hematopoietic stem cells (LT-HSCs) as well as their homing and engraftment to the bone marrow, the inhibition of angiogenesis, and the maintenance of differentiation potency of muscle satellite and cardiac stem-progenitor cells [32]. This review provides insights on the recently discovered function and role of CD82 and explores future research directions.

***Corresponding author**
Tel : +82-51-510-8129, Fax : +82-51-510-8526
E-mail : gene44@pusan.ac.kr

CD82 as a tumor metastasis suppressor

CD82 is known as a metastasis suppressor that mainly inhibits cancer metastasis [21], and it can be observed that the expression of CD82 reduces in various malignancies, including colon, lung, pancreatic, prostate, breast, ovarian, and other cancers [12, 13, 38, 41]. Additionally, overexpression of CD82 suppresses cell migration and invasion *in vitro* and inhibits tumor metastasis *in vivo* [6, 40]. Cancer develops gradually by inducing angiogenesis and proliferation of cancer cells through the metastasis of malignant tumors [18, 29]. Cell adhesion molecules (CAMs), such as integrin and cadherin, are involved in the metastasis process, the start of cancer progression [18]. CD82 interacts with these CAMs to in-

hibit cancer cell migration, helps the formation of E-cadherin/β-catenin complex, and regulates laminin-binding through integrin-α6 [1]. Through these processes, it inhibits downstream signaling of integrin, such as the p130CAS-Crk complex, and prevents cancer cell metastasis by regulating cell-to-cell adhesion [1, 18, 21]. It has been reported that KITENIN (KAI1 COOH-terminal interacting tetraspanin) interacts with the C-terminal region of KAI1, the main part of metastasis suppressor function, and its expression is associated with cancer cell invasiveness [19]. It also inhibits cancer metastasis by combining the CD82 counter molecule DARC (Duffy antigen receptor for chemokines) protein expressed in endothelial cells (ECs) and CD82 on the cancer cell surface, causing cancer cells to senescence and prevent passage through the vascular wall [3, 42]. The critical step of metastasis is the ability of tumor cells to survive. It has been reported that Gp78 influences ubiquitin-mediated proteasomal degradation of CD82. Furthermore, inhibition of Gp78 leads to augmentation of metastatic function of KAI1 and promoting tumor cell death [37]. As a therapeutic approach against cancer, it is important to elucidate the regulatory mechanism of cancer invasion and metastasis, especially the regulatory mechanism of CD82 expression, which is important for targeting CD82. A study on the regulatory mechanism of CD82 gene expression revealed an alternative splice form in which exon7 of CD82 was removed; the study reported that the spliced CD82 did not efficiently inhibit metastasis in gastric carcinoma compared with wild-type CD82 [20]. In addition, the transcriptional regulation of CD82 expression involves various transcription repressors and transcription activators [21]. The p50 subunit of NFκB, a nuclear transcription factor, binds to the CD82 promoter; moreover, it has been reported that NFκB activation increases the mRNA and protein levels of CD82 in various adenocarcinoma cell lines [33]. It is also known that the β-catenin-reptin complex binds to the p50 subunit docked in the NFκB response of the CD82 promoter region and replaces the Tip60 co-activator complex to inhibit CD82 transcription [16]. It is known that the binding sites for transcription factors, such as p53, Sp1, AP1, and AP2, exist in the CD82 promoter [5] and that c-Jun and Jun-B have also been implicated in the transcriptional regulation of CD82 [24, 25].

The role of CD82 in bone marrow stem cell niche

HSCs are mainly in the bone marrow and are eventually differentiated into lymphocytes and myeloid cells through LT-HSCs, short-term repopulating HSCs (ST-HSCs), and multipotential progenitors (MPPs) [7]. The stem cell niche is an *in vivo* microenvironment that enables self-renewal, differentiation, quiescence, and activation of stem cells to be controlled according to the body's circumstances, thereby maintaining homeostasis [30]. There are various niche-supporting cells in the bone marrow constituting the niche of hematopoietic stem cells. Niche-supporting cells include osteoblasts, mesenchymal stromal cells (MSCs), sinusoidal ECs, CXCL12-abundant reticular cells (CAR cells), and macrophages, reported to regulate self-renewal, proliferation, dormancy, and differentiation of HSCs *in vivo* and *in vitro* [8]. It has been reported that CD82 is predominantly expressed in the most undifferentiated and regenerating LT-HSCs present in the bone marrow, and cell cycle regulated by DARC-expressing macrophages [14, 15]. It was found that CD82 maintains the dormancy of HSCs by interacting with DARC [15]. LT-HSCs are maintained in a dormant state in bone marrow by autocrine signaling and paracrine factors [28]. It has been reported that CD82 is downstream of TGF-β (transforming growth factor-β) and is secreted from LT-HSCs and MSCs to induce stem cells into a dormant state [15]. HSCs are mostly maintained in the bone marrow, circulate at low density in the peripheral blood, and migrate to the bone marrow by homing [27]. This is known as an important step to repopulate the bone marrow after stem cell transplantation in stem cell therapy, and the goal of successful transplantation depends on the efficient return and engraftment of HSCs to the bone marrow [31]. In leukemic cells, CD82 promotes N-cadherin clusters in cell membranes, facilitating the return to the bone marrow [23]. Additionally, CD82 enhances the return of HSCs to the bone marrow required for engraftment through the regulation of Rac1 activation [9]. CD82 increases the expression of integrin α4β1 and cluster formation, thereby increasing adhesion to the microenvironment of the bone marrow [36]. Therefore, CD82 could be used as an essential functional marker in HSCs and could be a therapeutic target to improve the efficacy of HSC transplantation therapy.

The role of CD82 in muscle stem cells

Identification of muscle stem cell-specific surface markers is essential for studying the function of muscle satellite cells,

which are essential for muscle differentiation and regeneration. It has been reported that tetraspanins such as CD9, CD53, and CD81 are involved in muscle differentiation, and muscle cell fusion in skeletal muscle, and CD82 has also been reported to function in muscle stem cells [10, 22]. It was found that CD82 regulates the growth and quiescence of muscle satellite cells through the complex with proteins such as α7-integrin and α-sarcoglycan [2, 10]. *In vitro* and *in vivo*, myotube formation in muscle satellite cells was increased according to the expression of CD82, and the proliferation potential of satellite cells was also maintained high. Also, in the Duchenne muscular dystrophy model, it was reported that the expression of CD82 is reduced, and the absence of α7-integrin induces muscle dystrophy [2, 26]. This suggests that CD82 maintains the differentiation potential of muscle satellite cells and is important for muscle stem cell function in muscle diseases such as muscular dystrophy. In addition to muscle stem cells, it was found that cardiomyocyte progenitor cells derived from human-induced pluripotent stem cells (hiPSCs) also express CD82. CD82 is temporarily expressed in late-stage mesoderm cells during hiPSCs differentiation. Overexpression of CD82 in undifferentiated hiPSCs resulted in the differentiation into cardiomyocytes through inhibition of Wnt signaling [34]. Altogether, these results suggest that CD82 is involved in maintaining the differentiation potential of muscle satellite cells and determining the differentiation fate of stem-progenitor cells in cardiac muscle.

The role of CD82 in angiogenesis

There have been several studies on the relationship between angiogenesis and inflammation in pathological situations [4]. Angiogenesis is essential for the removal of pathogens and tissue regeneration through induction of inflammation, but still a considerable factor during treatment due to its association with disease progressions, such as cancer, age-related macular degeneration, and chronic inflammation [4]. Although CD82 is expressed in various vascular ECs, little is known about its role in vascular function. CD82 induces the endocytosis of CAMs by regulating gangliosides, CAMs-membrane microdomain interactions, and lipid raft clustering in the plasma membrane of vascular ECs [4, 39]. This removes CAM, such as CD44, and inhibits the migration and invasion of vascular ECs, inhibiting angiogenesis [39]. Additionally, it was found that CD82 inhibits the expression of IL-6 and VEGF in melanoma to prevent angiogenesis [35]. Therefore, elucidating the roles of CD82 in the molecular mechanism between angiogenesis and inflammation could be a novel therapeutic approach for chronic inflammatory diseases and cancer. Furthermore, in addition to the role of CD82 in vascular ECs, studies elucidating the role of CD82 in perivascular cells are required to better understand the role of CD82 in angiogenesis.

Discussion

Tetraspanins are transmembrane proteins expressed in almost all eukaryotic cells and are involved in regulating several proteins, such as integrins, cell surface receptors, and signaling molecules [11, 21]. As a molecular facilitator, tetraspanin interacts with various types of tetraspanin and proteins present in the cell membrane and cytoplasm through the formation of tetraspanin-enriched microdomains. This review dealt in depth with the role of CD82, which has been studied extensively among tetraspanins and has been identified as a key marker for blood stem cells, muscle progenitors, and cardiac progenitors, as well as a cancer metastasis suppressor (Fig. 1). Recent studies have revealed the function of CD82 as a pivotal cell surface protein that can distinguish their hierarchies in stem-progenitor cells of various tissues and organs [2, 15, 34]. In cell therapy for patient treatment, identifying cell surface proteins expressed on the cell membrane is more valuable than simple gene expression or protein expression in the cytoplasm. This can be used when the target cells for cell therapy are separated from the bone marrow or blood by flow cytometry or magnetic cell separation and amplified according to the therapeutic capacity. Therefore, the identification of CD82 expression and elucidating its role in stem-progenitor cells of various organs are very important in terms of amplification and verification of cellular resources in stem cell therapy. In addition, the analysis of the expression of CD82 and other tetraspanins in stem-progenitor cells of organs other than blood, vessels, muscles, and heart remains a major challenge. Although the DARC molecule, which is expressed in ECs, erythrocytes, and macrophages [15, 42], is currently known as the receptor for CD82, finding new binding partners of CD82 that are different from the CD82-DARC signaling axis and elucidating new signaling mechanisms remain a big challenge. Therefore, in addition to CD82, elucidating the functions and mechanisms of other tetraspanins can be directly related to treating vari-

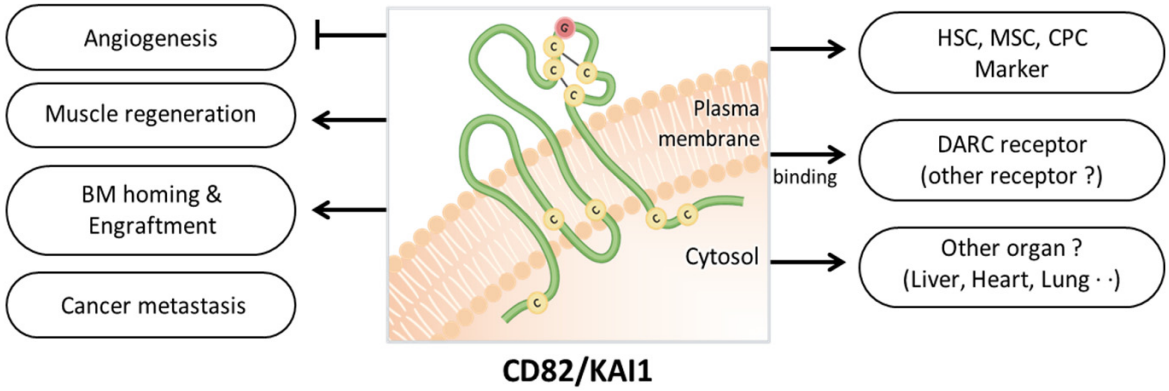

Fig. 1. Schematic of various CD82 molecular functions. CD82, a stem cell marker, performs the stem cell niche function through binding with DARC and affects the homing and engraftment of HSCs to the bone marrow. Additionally, it plays various roles, such as inhibition of metastasis of cancer cells, inhibition of angiogenesis, and muscle regeneration. Further studies on the role of CD82 and its interaction with other proteins are needed.

ous diseases and will further improve the quality of human life.

Acknowledgment

This work was supported by a 2-Year Research Grant of Pusan National University.

The Conflict of Interest Statement

The authors declare that they have no conflicts of interest with the contents of this article.

References

1. Abe, M., Sugiura, T., Takahashi, M., Ishii, K., Shimoda, M. and Shirasuna, K. 2008. A novel function of CD82/KAI-1 on E-cadherin-mediated homophilic cellular adhesion of cancer cells. *Cancer Lett.* **266**, 163-170.
2. Alexander, M. S., Rozkalne, A., Colletta, A., Spinazzola, J. M., Johnson, S., Rahimov, F., Meng, H., Lawlor, M. W., Estrella, E., Kunkel, L. M. and Gussoni, E. 2016. CD82 is a marker for prospective isolation of human muscle satellite cells and is linked to muscular dystrophies. *Cell Stem Cell* **19**, 800-807.
3. Bandyopadhyay, S., Zhan, R., Chaudhuri, A., Watabe, M., Pai, S. K., Hirota, S., Hosobe, S., Tsukada, T., Miura, K., Takano, Y., Saito, K., Pauza, M. E., Hayashi, S., Wang, Y., Mohinta, S., Mashimo, T., Iiizumi, M., Furuta, E. and Watabe, K. 2006. Interaction of KAI1 on tumor cells with DARC on vascular endothelium leads to metastasis suppression. *Nat. Med.* **12**, 933-938.
4. Costa, C., Incio, J. and Soares, R. 2007. Angiogenesis and chronic inflammation: cause or consequence? *Angiogenesis* **10**, 149-166.
5. Dong, J. T., Isaacs, W. B., Barrett, J. C. and Isaacs, J. T. 1997. Genomic organization of the human KAI1 metastasis-suppressor gene. *Genomics* **41**, 25-32.
6. Dong, J. T., Lamb, P. W., Rinker-Schaeffer, C. W., Vukanovic, J., Ichikawa, T., Isaacs, J. T. and Barrett, J. C. 1995. KAI1, a metastasis suppressor gene for prostate cancer on human chromosome 11p11.2. *Science* **268**, 846-884.
7. Dykstra, B., Kent, D., Bowie, M., McCaffrey, L., Hamilton, M., Lyons, K., Lee, S. J., Brinkman, R. and Eaves, C. 2007. Long-term propagation of distinct hematopoietic differentiation programs *in vivo*. *Cell Stem Cell* **1**, 218-229.
8. Ehninger, A. and Trumpp, A. 2011. The bone marrow stem cell niche grows up: mesenchymal stem cells and macrophages move in. *J. Exp. Med.* **208**, 421-428.
9. Ferraro, F., Celso, C. L. and Scadden, D. 2010. Adult stem cels and their niches. *Adv. Exp. Med. Biol.* **695**, 155-168.
10. Gnocchi, V. F., White, R. B., Ono, Y., Ellis, J. A. and Zammit, P. S. 2009. Further characterisation of the molecular signature of quiescent and activated mouse muscle satellite cells. *PLoS One* **4**, e5205.
11. Hemler, M. E. 2005. Tetraspanin functions and associated microdomains. *Nat. Rev. Mol. Cell Biol.* **6**, 801-811.
12. Hinoda, Y., Adachi, Y., Takaoka, A., Mitsuuchi, H., Satoh, Y., Itoh, F., Kondoh, Y. and Imai, K. 1998. Decreased expression of the metastasis suppressor gene KAI1 in gastric cancer. *Cancer Lett.* **129**, 229-234.
13. Huang, C. I., Kohno, N., Ogawa, E., Adachi, M., Taki, T. and Miyake, M. 1998. Correlation of reduction in MRP-1/CD9 and KAI1/CD82 expression with recurrences in breast cancer patients. *Am. J. Pathol.* **153**, 973-983.
14. Hur, J., Baek, S. H. and Kim, H. S. 2016. KAI1(CD82)-DARC(CD234) axis in the stem cell niche. *Cell Cycle* **15**, 1945-1947.
15. Hur, J., Choi, J. I., Lee, H., Nham, P., Kim, T. W., Chae, C. W., Yun, J. Y., Kang, J. A., Kang, J., Lee, S. E., Yoon, C. H., Boo, K., Ham, S., Roh, T. Y., Jun, J. K., Lee, H., Baek,

S. H. and Kim, H. S. 2016. CD82/KAI1 Maintains the dormancy of long-term hematopoietic stem cells through interaction with DARC-expressing macrophages. *Cell Stem Cell* **18**, 508-521.
16. Kim, J. H., Kim, B., Cai, L., Choi, H. J., Ohgi, K. A., Tran, C., Chen, C., Chung, C. H., Huber, O., Rose, D. W., Sawyers, C. L., Rosenfeld, M. G. and Baek, S. H. 2005. Transcriptional regulation of a metastasis suppressor gene by Tip60 and β-catenin complexes. *Nature* **434**, 921-926.
17. Lebel-Binay, S., Lagaudriere, C., Fradelizi, D. and Conjeaud, H. 1995. CD82, member of the tetra-span-transmembrane protein family, is a costimulatory protein for T cell activation. *J. Immunol.* **155**, 101-110.
18. Lee, H. A., Park, I., Byun, H. J., Jeoung, D., Kim, Y. M. and Lee, H. 2011. Metastasis suppressor KAI1/CD82 attenuates the matrix adhesion of human prostate cancer cells by suppressing fibronectin expression and beta1 integrin activation. *Cell Physiol. Biochem.* **27**, 575-586.
19. Lee, J. H., Park, S. R., Chay, K. O., Seo, Y. W., Kook, H., Ahn, K. Y., Kim, Y. J. and Kim, K. K. 2004. KAI1 COOH-terminal interacting tetraspanin (KITENIN), a member of the tetraspanin family, interacts with KAI1, a tumor metastasis suppressor, and enhances metastasis of cancer. *Cancer Res.* **64**, 4235-4243.
20. Lee, J. H., Seo, Y., Park, S. R., Kim, Y. J. and Kim, K. K. 2003. Expression of a splice variant of KAI1, a tumor metastasis suppressor gene, influences tumor invasion and progression. *Cancer Res.* **63**, 7247-7255.
21. Liu, W. M. and Zhang, X. A. 2006. KAI1/CD82, a tumor metastasis suppressor. *Cancer Lett.* **240**, 183-194.
22. Liu, Q. C., Zha, X. H., Faralli, H., Yin, H., Louis-Jeune, C., Perdiguero, E., Pranckeviciene, E., Munoz-Canoves, P., Rudnicki, M. A., Brand, M., Perez-Iratxeta, C. and Dilworth, F. J. 2012. Comparative expression profiling identifies differential roles for Myogenin and p38a MAPK signaling in myogenesis. *J. Mol. Cell Biol.* **4**, 386-397.
23. Marjon, K. D., Termini, C. M., Karlen, K. L., Saito-Reis, C., Soria, C. E., Lidke, K. A. and Gillette, J. M. 2016. Tetraspanin CD82 regulates bone marrow homing of acute myeloid leukemia by modulating the molecular organization of N-cadherin. *Oncogene* **35**, 4132-4140.
24. Marreiros, A., Dudgeon, K., Dao, V., Grimm, M. O., Czolij, R., Crossley, M. and Jackson, P. 2005. KAI1 promoter activity is dependent on p53, junB and AP2: evidence for a possible mechanism underlying loss of KAI1 expression in cancer cells. *Oncogene* **24**, 637-649.
25. Mashimo, T., Bandyopadhyay, S., Goodarzi, G., Watabe, M., Pai, S. K., Gross, S. C. and Watabe, K. 2000. Activation of the tumor metastasis suppressor gene, KAI1, by etoposide is mediated by p53 and c-Jun genes. *Biochem. Biophys. Res. Commun.* **274**, 370-376.
26. Mayer, U., Saher, G., Fassler, R., Bornemann, A., Echtermeyer, F., von der Mark, H., Miosge, N., Poschl, E. and von der Mark, K. 1997. Absence of integrin alpha 7 causes a novel form of muscular dystrophy. *Nat. Genet.* **17**, 318-323.
27. Mazo, I. B. and von Andrian, U. H. 1999. Adhesion and homing of blood-borne cells in bone marrow microvessels. *J. Leukoc. Biol.* **66**, 25-32.
28. Nham, P., Choi, J. I., Hur, J., Baek, S. H. and Kim, H. S. 2017. Shedding light on the DARC knight as a guardian of hematopoietic stem cell quiescence. *Stem Cell Investig.* **4**, 8.
29. Odintsova, E., Sugiura, T. and Berditchevski, F. 2000. Attenuation of EGF receptor signaling by a metastasis suppressor, the tetraspanin CD82/KAI-1. *Curr. Biol.* **10**, 1009-1012.
30. Jurecic, R., Li, L. and Humphries, R. K. 2012. Heterogeneity, self-renewal, and differentiation of hematopoietic stem cells. *Stem Cells Int.* **2012,** 1-2.
31. Sahin, A. O. and Buitenhuis, M. 2012. Molecular mechanisms underlying adhesion and migration of hematopoietic stem cells. *Cell Adh. Migr.* **6**, 39-48.
32. Saito-Reis, C. A., Marjon, K. D., Pascetti, E. M., Floren, M. and Gillette, J. M. 2018. The tetraspanin CD82 regulates bone marrow homing and engraftment of hematopoietic stem and progenitor cells. *Mol. Biol. Cell.* **29**, 2946-2958.
33. Shinohara, T., Miki, T., Nishimura, N., Nokihara, H., Hamada, H., Mukaida, N. and Sone, S. 2001. Nuclear factor-kappaB-dependent expression of metastasis suppressor KAI1/CD82 gene in lung cancer cell lines expressing mutant p53. *Cancer Res.* **61**, 673-678.
34. Takeda, M., Kanki, Y., Masumoto, H., Funakoshi, S., Hatani, T., Fukushima, S., Izumi-Taguchi, A., Matsui, Y., Shimamura, T., Yoshida, Y. and Yamashita, J. K. 2018. Identification of cardiomyocyte-fated progenitors from human-induced pluripotent stem cells marked with CD82. *Cell Rep.* **22**, 546-556.
35. Tang, Y., Bhandaru, M., Cheng, Y., Lu, J., Li, G. and Ong, C. J. 2015. The role of the metastasis suppressor gene KAI1 in melanoma angiogenesis. *Pigment Cell Melanoma Res.* **28**, 696-706.
36. Termini, C. M., Cotter, M. L., Marjon, K. D., Buranda, T., Lidke, K. A. and Gillette, J. M. 2014. The membrane scaffold CD82 regulates cell adhesion by altering alpha4 integrin stability and molecular density. *Mol. Biol. Cell* **25**, 1560-1573.
37. Tsai, Y. C., Mendoza, A., Mariano, J. M., Zhou, M., Kostova, Z., Chen, B., Veenstra, T., Hewitt, S. M., Helman, L. J., Khanna, C. and Weissman, A. M. 2007. The ubiquitin ligase gp78 promotes sarcoma metastasis by targeting KAI1 for degradation. *Nat. Med.* **13**, 1504-1509.
38. Tsai, Y. C. and Weissman, A. M. 2011. Dissecting the Diverse Functions of the Metastasis Suppressor CD82/KAI1. *FEBS Lett.* **585**, 3166-3173.
39. Wei, Q., Zhang, F., Richardson, M. M., Roy, N. H., Rodgers, W., Liu, Y., Zhao, W., Fu, C., Ding, Y., Huang, C., Chen, Y., Sun, Y., Ding, L., Hu, Y., Ma, J. X., Boulton, M. E., Pasula, S., Wren, J. D., Tanaka, S., Huang, X., Thali, M., Hammerling, G. J. and Zhang, X. A. 2014. CD82 restrains pathological angiogenesis by altering lipid raft clustering and CD44 trafficking in endothelial cells. *Circulation* **130**, 1493-1504.
40. Yang, X., Wei, L. L., Tang, C., Slack, R., Mueller, S. and Lippman, M. E. 2001. Overexpression of KAI1 suppresses *in vitro* invasiveness and *in vivo* metastasis in breast cancer cells. *Cancer Res.* **61**, 5284-5288.

41. Yu, Y., Yang, J. L., Markovic, B., Jackson, P., Yardley, G., Barrett, J. and Russell, P. J. 1997. Loss of KAI1 messenger RNA expression in both high-grade and invasive human bladder cancers. *Clin. Cancer Res.* **3**, 1045-1049.

42. Zijlstra, A. and Quigley, J. P. 2006. The DARC side of metastasis: shining a light on KAI1-mediated metastasis suppression in the vascular tunnel. *Cancer Cell* **10**, 177-178.

초록 : 분자 촉진제를 넘어, CD82: 전이억제자, 줄기세포 니쉬, 근육 재생 및 혈관신생에서의 역할

이현채[1] · 한정화[1,2] · 허진[1,2]*

([1]부산대학교 의과대학 융합의과학과, [2]PNU GRAND 융합의과학 교육연구단)

CD82/KAI1은 분자촉진제로서 암 전이억제자로 역할이 잘 알려져 있으나, 최근 줄기 전구 세포와 혈관 신생, 근육에서 다양한 역할들이 밝혀지고 있다. 이에 본 연구진은 최근에 보고된 CD82의 다양한 기능과 역할에 관하여 총설 하고자 한다. CD82는 4개의 막 통과 도메인을 가진 테트라스파닌의 한 종류로 암의 전이 과정에 관여하는 세포접착분자들과의 상호작용을 통하여 암세포의 이동 능력을 저해한다. 암 전이 억제자로의 기능 외에도 줄기세포 니쉬에서도 그 역할이 밝혀졌다. 골수에서 분화재생능력이 뛰어난 최상위 조혈모세포(LT-HSC)에서 CD82가 발현되며, DARC와의 상호결합으로 줄기세포의 휴면을 유도한다. 줄기세포의 휴면 조절 외에도, CD82는 Rac1 활성 조절을 통해 조혈모세포의 골수로의 귀환 및 생착에도 역할을 한다. 또한, CD82는 근육 줄기 세포의 분화능을 유지시키며, 혈관 내피세포에서 세포 접착 분자와 IL-6, VEGF와 같은 사이토카인의 발현을 저해하여 혈관 신생을 억제한다. CD82는 다양한 조직 및 줄기-전구 세포에서 계급을 구별할 수 있는 핵심 세포막 표면 단백질이며, 세포 자원의 증폭 및 검증에 있어 중요하다. 다양한 기관과 세포에서 CD82의 역할과 추가적인 연구들이 줄기세포 치료의 임상적 적용에 있어 큰 도움이 되기를 기대한다.