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REVIEW ARTICLE

Specific Protein Markers for Stem Cell Cross-Talk with Neighboring Cells in the Environment

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A stem cell interacts with the neighboring cells in its environment. To maintain a living organism's metabolism, either cell-cell or cell-environment interactions may be significant. Usually, these cells communicate with each other through biological signaling by interactive behaviors of primary proteins or complementary chemicals. The signaling intermediates offer the stem cell's functionality on its metabolism. With the rapid advent of omics technologies, various specific markers by which stem cells cooperate with their surroundings have been discovered and established. In this article, we review several stem cell markers used to communicate with either cancer or immune cells in the human body.

Keywords: Cancer cell, Immune cell, Protein marker, Signaling cross-talk, Stem cell

Stem Cells and Their Adjacent Environments

A stem cell is generally defined as a biological cell that can divide and differentiate into diverse cell types (1). In particular, stem cells possess two distinctive features: potency and self-renewal. In mammals, adults produce some stem cells to repair injured parts of the body, while developing embryos make stem cells for specialized cell differentiation and also to maintain regenerative organs. They are highly potent for any type of tissue regeneration.

There are two species of stem cells: embryonic and adult stem cells. To date, adult cells, such as epithelial cells, are interestingly reprogrammed into stem cells with pluripotent capabilities. They are simply manufactured via an inclusion of some transcription codes (e.g., Oct3/4, Sox2, c-Myc, Klf4, Nanog, or Lin28) to adult cells (2). Table 1 depicts the process that some adult cells undertake to become induced stem cells.

Owing to the unique characteristics that may be represented by cell potency and renewal, stem cells have been topics of great interest in therapeutic and regenerative medicine fields. They may become a main component for next-generation therapies where the injured or diseased organs of patients are replaced by new alternatives grown via stem cell methods. To understand the working mechanism of therapeutic stem cells, it might be helpful to determine the surface markers at the interfaces between stem cells and their neighbors (Fig. 1).

With the advent of genomics and proteomics, a variety of stem cell markers have been identified. Table 1 shows a list of genes and protein products used to identify various stem cells.

In this review, we focused more on the stem cell markers at the interface between a stem cell and its environment, especially in the following two cases: the interaction between stem cells and immune cells in the surroundings of cancerous tumors, and the interaction between stem

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Table 1. A list of protein markers on some types of stem cells (Reproduced from R&D system®)

Name	Species	Specification	Reference
Oct-3/4	Embryonic stem cell	- POU transcription factor - It sustains stem cells'self-renewal and pluripotency	61～65
SSEMAs (Stage Specific Embryonic Antigens)	Embryonic stem cell	- Carbohydrate-associated - It controls cell surface interaction during development	66～73
CD34	Hematopoietic stem cell	- The most critical marker - It exclude more primitive stem cells	74～88
CD133	Hematopoietic stem cell	- An alternative to CD34 for HSC selection and ex vivo expansion	89～93
ABCG2	Hematopoietic stem cell	- ATP-binding cassette superfamily G member - First identified in a breast cancer cell line - It implicate a functional role in developmental stem cell biology	35, 94～99
Sca-1	Hematopoietic stem cell	- 18 kDa phosphatidylinositol-anchored protein - It is used to enrich progenitor cell populations and also regulate both B and T cell on activation	100～111
STRO-1	Mesenchymal/Stromal stem cell	- It is a valuable Ab for the identification, isolation and functional characterization of human bone marrow stromal cell precusors	112～116
Nestin	Neural stem cell	- A class VI intermediate filament protein - Its function is undefined	117～130
PSA-NCAM (polysialic acid-neural cell adhesion molecule)	Neural stem cell	- Critical for many neural developmental processes and highly polysialylated - It is related to synaptic rearrangement and plasticity	131～139
p75 Neurotrophin R (NTR)	Neural stem cell	- A type I transmembrane protein that belongs to the tumor necrosis factor receptor superfamily - It enhances responses to neurotrophin	140～147

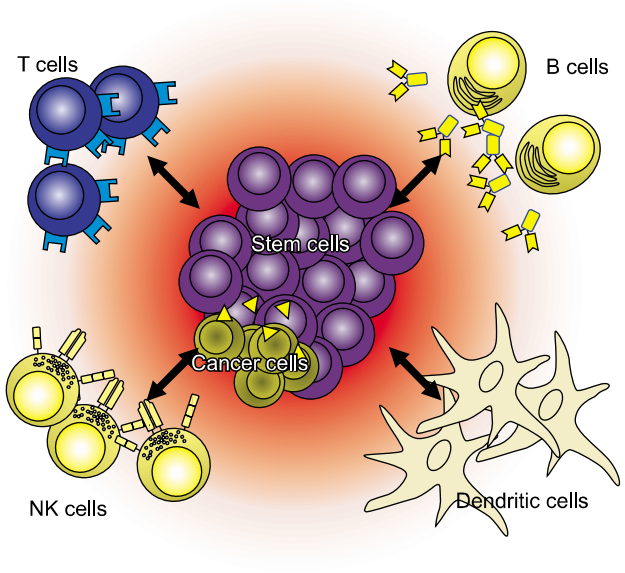

Fig. 1. Schematic representation of stem cell cross-talk with neighboring cells in the environment.

cells and cancers.

Specific Markers for Stem Cell Cross-Talk at the Moment when the Stem Cells Come in Contact with Cancer

All cells interact with their surrounding microenvironment, including cancer cells (3). Therefore, detecting the interaction of cancer cells with their surroundings has become a powerful theragnostic method. Many studies have been conducted that have focused on the nature of tumorigenesis, which generally falls into more than one of the following mechanisms: self-sufficient proliferation, insensitivity toward growth suppressors, invasion and metastasis, angiogenesis, resistance to apoptosis, and immortality via limitless replication (4). All these mechanisms are closely related with cell-microenvironment interactions where there have been miscommunications initiated by genomic errors.

For example, certain types of cancer cells generate their own growth signals, such as transforming growth factor alpha (TGF-α). Therefore, these cancer cells upregulate the TGF-α gene. Another transforming growth factor, TGF-β,

is secreted by metastatic melanoma. TGF-β allows cancer cells to hide from a person's innate immune system by hindering the activities of natural killer cells and T lymphocytes. As a result, the tumor is not recognized as non-self by the immune system, which makes it difficult to use conventional immunotherapy to treat this type of cancer. Changes that occur in the extracellular matrix also may lead to neoplasia (5, 6).

Angiogenesis is one of many distinct characteristics of cancer cells during tumor formation. At the initial state of tumorigenesis, hypoxia occurs within the cells. Cancer cells extend their vasculature into their surroundings to provide the oxygen-rich nutrients necessary for proliferation and growth. Some studies have claimed that hypoxia leads to transcription of hypoxia-inducible factor-1 (HIF-1), which in turn promotes the expression of angiogenic factors (7, 8). The typical examples of those angiogenic factors include vascular endothelial growth factors (VEGF), fibroblast growth factors (FGF) and placenta-like growth factors (PLGF). A myriad of other factors contribute to vascular formation, even those that are not specific for the vascular endothelium (9).

As described above, no matter how and where the tumorigenesis has been initiated, genomic instability drives the corresponding characteristic gene expression, which can be understood as a way for cells to communicate with their surroundings. Therefore, examining these communication signals makes it possible to observe any differentiation of cancer cells from normal cells and even to evaluate the cancer status; numerous scientists have investigated whether the progression of preneoplasia to cancer can be detected using these signals, which include antibodies, peptides and other chemicals (10). However, these signals are not unique chemicals that only cancer cells exhibit; normal cells, too, release them into their surroundings. The distinctive feature of cancer cells is that they overexpress certain genes compared to the normal cells. This overexpressing characteristic becomes a lighthouse for targeting ligands of drug carriers, which became the core principle in active targeting drug delivery to cancer cells. For example, the luteinizing hormone-releasing hormone (LHRH) receptor is one target that could be bound by LHRH peptide, one of the targeting peptides (11). LHRH receptors are overexpressed by several types of cancer cells, including those of breast, ovarian and prostate cancer (12-14). Therefore, such cancer cells can be selectively bound by LHRH peptide, increasing the specific binding ability of drug carriers that use the LHRH peptide as a targeting ligand. In a similar fashion, SP94, one of the targeting peptides that specifically binds to unknown receptors present on the surface of human hepatocellular carcinoma, has been applied as a ligand in several drug delivery cases (15, 16). The receptor that the SP94 peptide targets is not yet specified-it has only been identified by performing a filamentous phage display, which is a powerful tool for selecting a specific peptide that has a high affinity towards certain cancer cells from a pool of random peptides.

It should be noted that certain types of cancer cells exhibit multiple characteristic signals, and these signals may overlap with those from different cancer cell types. Even cancers from the same origin may exhibit different gene overexpression trends. For example, prostate cancers overexpress LHRH receptors and also androgen receptors (AR) at the same time (17). However, while LNCaP, one of the human prostate adenocarcinomas, is androgen-sensitive, PC3, which is another type of the same cancer, does not show such sensitivity (18). Certain breast cancer cells exhibit an HER2 sensitive phenotype, while others do not.

Consequently, it is necessary to take into account the type of cancer, the degree to which the characteristic overexpression is exhibited and in what combination would multiple overexpressions be expressed to maximize the tumor target specificity when selecting a targeting material. Table 2 displays a list of targeting materials and their targeted tumors.

In 2002, Sooryanarayana Varambally et al. reported that a polycomb group protein enhancer of zeste homolog 2 (EZH2) was overexpressed in hormone-refractory metastatic prostate cancer (19). In addition to simply examining EZH2 overexpression, they also observed increments in the degree of overexpression as the cancer progressed from benign, prostatic atrophy, prostatic intraepithelial neoplasia, clinically localized prostate cancer, and finally metastatic prostate cancer. Therefore, this finding suggests the possibility of predicting the cancer's progression by examining the correlation between the amounts of EZH2 protein and the aggressiveness of the type of prostate cancer.

The conventional way of delivering drugs to cancer cells has mainly been via a passive targeting method rather than through active targeting drug delivery via the characteristic biochemical signals released by cancer cells. This passive targeting also bases its principle on microenvironment features exhibited by cancer cells. As a tumor grows, angiogenesis progresses and leads to consequent abnormalities in the vasculature. One of the important features of this abnormality is fenestrated vasculature (20). Through the gaps that form from the loosened capillary vessels, small molecules, such as drugs, with sizes of less than a

Table 2. A list of targeting materials and the targeted tumor

Target tumor	Targeting material	Target receptor	Reference
Human colon (HCT116)	IFLLWQR (IF7) (peptide)	Annexin 1 (anxa1)	148
B16 Melanoma	YIGSR (peptide)	Laminin receptor	149
Ovarian, breast, prostate carcinomas	LHRH peptide	LHRH receptor	11
Various cancer types	VNTANST (peptide)	Vimentin	150,151
B16F10	RGDGW (peptide)	$\alpha 5\beta 1$ integrin	152
Prostate carcinoma	F77 (mAb)	Prostate specific glycolipid (PCLA)	153
Hepatocellular carcinoma	SP94 (peptide)	Unknown	16
Hepatocellular carcinoma	FQHPSFI (HCBP1) (peptide)	Unknown	154
Lung (H640, A549 and H226)	CSNIDARAC (peptide)	EGF receptor (under research)	155
Breast cancer	CTCE-9908	CXCR4	156
Metastatic melanoma	SB505124	TGF-β	5

few nanometers may penetrate and accumulate at the tumor sites, which is called an enhanced permeability and retention (EPR) of the tumor. Regardless of how great this EPR effect from leaky vasculature near the cancer is, a majority of the drugs (>95%) still flows to and accumulates in other parts of the body, such as the liver, spleen and lungs (21). Therefore, active targeting needs to be investigated, and adequate selection for a targeting ligand will also be critical.

Specific Markers for Stem Cell Cross-Talk at the Moment When the Stem Cells Come in Contact With Immune Cells

Several diseases arise from the destruction or dysfunction of specific cells. Many attempts have been made to overcome these diseases. For instance, Parkinson's disease (22, 23), Huntington's disease (24), amyotrophic lateral sclerosis (25-28), Alzheimer's disease (29), spinal cord injury (30), brain tumor (31), lysosomal storage diseases (32), liver (33) and heart failure (34), Duchenne's muscular dystrophy (35), and osteogenesis imperfecta (36) are all target diseases of stem cell therapy. In these cases, treatment with stem cells that can differentiate into the damaged cell types can be effective.

Stem cell therapy mainly uses mesenchymal stem cells (MSC), neural stem cells (NSC) and embryonic stem cells (ESC) (37). When stem cells are delivered to the injury site or the targeted site for substituting functional cells, it is essential that they encounter the immune system of the host, including both the innate and adaptive immune system (38).

When the immune system comes in contact with forward-facing stem cells, some immune cells prepare for defense. Accordingly, T cells, B cells, dendritic cells, and NK cells create adaptive immunity against foreign materials. These immune cells play a part as well in stem cell treatments (38). Stem cells in the treatment area are recognized by activated immune cells as foreign and then become their targets. One of the most important variables is suppressing any immune rejection of stem cells (39) to maintain sufficient stem cell viability in the host system until the therapeutic effects are achieved.

Interestingly, some kinds of stem cells can overcome severe environmental conditions by suppressing the host immune system (39-41). By reducing host immune rejection, stem cells can have enough time to replicate themselves and differentiate into functional target cells. This immune suppression characteristic of stem cells has enormous potential to overcome the aforementioned serious diseases. Therefore, it is important to understand the interactions between the immune system and stem cells.

These interactions can be categorized by two different cell-to-cell communication methods. The first interaction category is based on cytokines. Most immune cells secrete their own cytokines when they run into foreign antigens or suspicious materials. The secreted cytokines warn the environmental cells, which recruit other immune cells. There are many types of cytokines, and their functions are deserving of further study (42). These cytokines affect both immune systems and treated stem cells. In injury situations or graft surgeries, accumulated or treated stem cells are exposed by cytokines of the host's immune system. By sensing these cytokines, stem cells regulate an immunological rejection (43-47). Cytokines secreted by T cells or other immune cells would be recognized by MSC, NSC and ESC. In the case of human MSC (hMSC), co-cultured B cells are arrested in the G0/G1 phase. B cell arrest is caused by soluble factors produced by the hMSC. In addition, receptors expressed by B cell, CXCR4, CXCR5, and CXCR7 are down-regulated (48). The NSC may be affected by cytokines, such as TNF-α or IL-6 (46,

Table 3. The interactions between immune cells and stem cells. Here note that SC designates stem cell and IM does immune cell

Stem cell	Immune cell	SC marker	IM marker	Cytokine	SC soluble factor	Interaction	Reference
Mesenchymal stem cell	T cell				NO	NO secreted from lisensed MSC, T cell suppression (mouse)	60
		CXCR5			CCR5	MSC secrets CXCR3 and CCR5 ligand	54
		ICAM-1, VCAM-1				ICAM-1 and VCAM-1 expression on MSC surface. T cell accumulation.	55
						naïve & memory T cell supression	157
		ICAM-1, VCAM-1, LFA-3				ICAM-1, VCAM-1, LFA-3 expression on MSC.	56
						Interacion with T cell	57
					IDO	MSC secret IDO, T cell suppression	158
							159
	B cell		CXCR4, CXCR5, CCR7			B cell CXCR4, CXCR5 and CCR7 down-regulation by soluble factors from hMSC	48
	Dendritic cell		CD83, CD80, CD86, HLA-DR, CD1a			Suppression of CD83, HLA-DR, CD80, CD86 and CD1a of DC by MSC	40
			CCR7, CD49dβ1			MSC supress CCR7 and CD49dβ1 on DC. Suppress DC immigration to lymph node.	160
	NK cell		NKp30, NKp44, NKG2D		IDO, prostaglandin E2	NK receptors, NKp30,NKp44 and NKG2D, suppressed by IDO and prostaglandin E2 secreted from MSC	161
					IDO	MSC secret IDO. NK cell suppression	159
Neural stem cell				CCL2, CXCL12		NSCs can recruit to injury site by CCL2 and CXCL12	162
		CCR2		MCP-1		In site of ischemia, CCR2 recognize MCP-1 and migration to ischemia	163
		TNFR1		TNF-α		TNF-a make p38 MAPK signaling pathway through TNFR1, cause apoptisis	49
		TNFR1		TNF-α		TNF-a activate IKK-β by TNFR1, increase NSC proliferation	50
		TNFR1, TNFR2		TNF-α		Suppress TNFR1, activate TNFR2. Increase neurogenesis	51
		CNTFR, LIFR, gp130				Renewal of NSC increase by CNTFR/LIFR/gp130-mediated signaling	52
		gp130		IL-6		IL-6 treated NSC more differentiate into astrocyte	46
		IL-1βR		IL-1β		IL-1β, produced by stress or directly treated, makes antineurogenetic effect	47
Embryonic stem cell		HLA-1				ESC has low level of HLA-1, shows lower Immunoreject	164
							165
		HLA-1				Immunoreject getting larger along with ESC differentiation.	166
		HLA-1		IFN-γ		In case of differentiated ESC, IFN-γ increases MHC expression and immunoreject	53
	NK cell		Activating NK receptor		NKG2D	ESC expressing NKG2D, activate NK cell and make strong rejection	167

49-51). With TNF-α, proliferation of NSC depends on the signal pathways. TNF-α signal via TNFR-1 induces apoptosis of NSC. TNFR-2, however, does not inhibit NSC proliferation (41). IL-6 affects NSC in two ways. First, IL-6 mediated via gp130 improves the self-renewal of NSC (52). Moreover, IL-6 treated NSC tends to differentiate into astrocytes (46). ESC also affects cytokines. The MHC expression level of ESC differentiated by 19 days is upregulated in the presence of IFN-γ. With undifferentiated ESC, however, there was no upregulation of MHC expression. ESC can increase its immunogenic profile via differentiation processes; therefore, less immune rejection occurs with the undifferentiated state of ESC (53).

Another category of interaction is based on surface markers expressed on the surface of stem/immune cells (40, 48, 54-57). In an immune response, several interactions are mediated by surface markers, such as T cell activation by dendritic cells (58) or infection recognition by cytotoxic T cells (59). Just like interactions between immune cells, markers expressed on stem cells can reduce immune reactions. In the case of MSC, inflammatory cytokines upregulate the expression of ICAM-1 and VCAM-1. These surface markers make MSC more adhesive to T cells. T cells accumulate around MSC, and the effect of NO produced by MSC (60) becomes more powerful. Thus, these two surface markers are used to suppress T cell activation and T cell apoptosis (54-57). These kinds of interactions are organized and adjusted in Table 3.

Conclusion

Currently, stem-cell medicine has the potential to provide effective treatments for a wide range of human diseases. This expectation has raised a new discipline, representative of either therapeutic or regenerative medicine. To deliver on the promise of stem-cell therapy, there is a need to increase our rudimentary understanding of how stem cells interact with neighboring cells, including immune cells or infected cells.

All of the approaches outlined in this article need to be pursued in parallel; it is likely that an interactive understanding of cells will provide the best result for all situations. There is much to be learned about the immune response to stem cells and cancer infection mechanisms in stem cell areas, and there will undoubtedly be many surprises as our understanding of this area increases.

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Potential conflict of interest

The authors have no conflicting financial interest.

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