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Targeting Cell Movement in Cardiovascular and Malignant Diseases

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Critical Role of Cell Movement in the Pathogenesis of Cardiovascular and Malignant Diseases

Besides cell mitogenecity, cell motogenecity is probably the most important cellular activity and prevalent cellular event involved in the initiation and development of cardiovascular and malignant diseases. Cell movement contributes to the pathogenesis of both malignant and cardiovascular diseases and directly correlates or determines the prognosis of patients with these diseases, thus making it an ideal therapeutic target. Cell motility and its markers can be used as diagnosis, prognosis, and staging markers for these two classes of diseases.

Cell movement not only drives the local invasion and infiltration of cancer cells but also is heavily involved in the local and distal metastasis. Epithelial-to-mesenchymal transition (EMT) drives the progression of most solid tumors (1) and is the motility-gaining process at the cellular level. Tumors undergone EMT typically exhibits high invasiveness and metastatic potential. Also, tumor-initiating cells or cancer stem cells typically possess high intrinsic locomotive potential in addition to the elevated survival, differentiation, and self-renewal capabilities (2).

For cardiovascular diseases, cell movement is critical for the development of common maladies such as atherosclerosis, restenosis, and vasculitis. Most of pathological cardiovascular cell movements in atherosclerosis and cardiac fibrosis are related to inflammation. Here cell movement determines the initiation and development of the disease; while in myocardial infarction and stroke, the cell movement responding to primary pathological damages directly affects the prognosis by initiating secondary pathological damages, such as cardiac fibrosis. Some cardiovascular diseases also involve endothelial-to-mesenchymal transition (EndoMT) resulting in cardiac fibrosis. Similar to EMT, increased cell movement is the most prominent feature of EndoMT.

Although increased cell motility is more often associated with malignant and cardiovascular diseases, reduced cell motility can also be found during the development of these diseases. For example, mesenchymal-to-epithelial transition (MET), accompanied by reduced cell

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movement, likely contributes to the settlement and colonization of circulating tumor cells and subsequent formation of metastatic lesion, while improper EndoMT with diminished motility of endothelial cells from the atrioventricular canal and outflow track during development causes invalvular insufficiency.

Targeting cell movement is critical for the successful treatment of cardiovascular and malignant diseases

Based on current mechanistic understanding of cardiovascular and malignant diseases, we predict that, in principle, targeting cell movement can either determine the successful treatment of both diseases, which are the major medical problems in current health care, or attenuate and mitigate their progression.

In cardiovascular diseases, the movement of endothelial, smooth muscle, and white blood cells typically follows acute or chronic inflammatory stimuli and causes subsequent damages in tissues and organs. Because inflammatory cell-movement events largely determine the pathogenesis of these diseases, blocking the infiltration of these cells will eventually benefit the patients.

Although the fatality of tumors typically results from invasion and metastasis, targeting cell movement in malignant diseases, however, has not been emphasized sufficiently because tumors are primarily considered as a disease of endless proliferation. Also, since cell movement has not been evaluated clinically or in clinical trials as an endpoint, it remains uncertain to what extent cell movement contributes to tumor progression and metastasis (3), despite the growing evidence supporting the critical role of tumor cell movement in metastasis. For malignant solid tumors, the cell movement-based therapy is predicted to block the spread of locally infiltrative cancers such as pancreatic cancer and glioma, dissemination of primary and metastatic cancer, and angiogenesis during tumor progression. Although recent observations underline the dissemination of tumor cells at early stage (4, 5), the new discoveries do not make the motility-inhibitory strategy less attractive but actually underpin it as a critical clinical preventive measure. Three types of cell movement are involved in tumor progression: tumor cell movement for local invasion and distal metastasis, vascular cell movement during tumor angiogenesis, and immune cell movement in tumor-initiated inflammation. It is clinically beneficial to target the first two kinds of cell movement but not the cell movement in immune response against tumor. Recent studies, however, indicate that macrophages in tumor microenvironment can induce and lead tumor cells to undergo intravasation (6), blurring the definition of therapeutic targets.

Because these key signaling events upregulate both mitogenic and motogenic activities, the approaches to target cell movement may also alter cell proliferation. For example, Src tyrosine kinases transmit integrin-dependent signals pivotal for cell movement and proliferation, while vascular endothelial growth factor (VEGF) promotes angiogenesis. Hence cell movement-based therapy may gain additional benefit clinically. Likewise, although some drugs used in the clinics or clinical trials were designed for other therapeutic purposes, such as anti-proliferation or antiangiogenesis, they also hold anti-motility property, and therefore their clinical benefits should partially attribute to the cell movement-targeting effect.

How to target cell movement in cardiovascular and malignant diseases?

The specificity of therapies against cell movement has become the prerequisite for successful drug intervention. Currently, a number of such approaches are under active investigation for delivery of small molecules, proteins and nucleic acids. Most therapeutic

approaches aim at inhibiting pathological cell movement associated with invasion and metastasis in tumor and inflammation in cardiovascular diseases.

At the molecular and cellular levels, the increased cell movement in malignant and cardiovascular diseases results from the combinatory effect of aberrant active intrinsic motility machinery and pathological motility-stimulatory milieu. Therefore, the strategies to selectively abrogate the pathological cell movement include the downregulation of the activity of cell intrinsic motility machinery and the blockade of cellular response to environmental motogenic cues. For example, restoring the function of cell motility suppressor and/or abrogating the function of cell motility enhancers are the basic strategy for targeted cell movement-based therapy against advanced cancers.

Specifically, cell movement can be targeted through tissue and cell events or processes such as cell-cell adhesion, EMT or EndoMT, intravasation or extravasation, and angiogenesis or lymphangiogenesis. In terms of the molecular and cellular target sites for cell movement, examples and candidates include stem or progenitor cell, membrane microdomain, kinase, and miRNA. Tactically, the therapeutic approaches against pathological cell movement include gene transfer, induction of suppressed gene expression, silencing of gene expression, and exogenous administration of gene product (7). Several drug delivery systems, including lipophilic and multifunctional polymeric carriers, novel nanoparticles, oncolytic viral carriers and bioconjugation have significant effect on cellular motility in cardiac and malignant diseases.

To provide the in-depth and latest insight into the cell movement-based therapy, we have assembled in this theme issue a cohort of articles revealing the mechanisms for pathological cell movement, drugable targets for cell movement-based therapy, and cutting-edge approaches for drug delivery. Although the information collected from these articles can be classified into the categories of targeting site design and targeting mean design, these categories are interconnected. For example, cell adhesion controls cell movement, and cell adhesion molecules can serve as drug targets to prevent tumor and inflammatory cell movement. Also, cell adhesion molecules can be used in theranostic imaging for local drug delivery (8).

This theme issue covers the critical aspects of pathological cell movement and the principles for its targeting in cardiovascular and malignant diseases. Palmer et al. and Veisheh et al. have highlighted the molecular determinants of tumor cell migration and invasion; while targeting miRNAs that regulate vascular cell movements has been discussed by Junming Yue. Mahato et al. focus on how bioconjugation of enzymes or antibodies to drug carriers can enhance antitumor effects of small molecules. Danquah et al. have discussed multifunctional polymeric carriers to overcome the physiological barriers set up by tissue microvasculature which hinders the efficacy of anticancer agents. Chua et al. have described EMT-based, novel therapeutics and approaches for the treatment of cancer and heart diseases. It is important to understand the role played by hypoxia-induced molecular changes in ischemic heart disease and Kim et al. have reviewed the applications of gene therapy to overcome ischemic heart diseases. Focal adhesion kinases are signaling molecules that are heavily involved in cell migration events and their role in angiogenesis in cancers is the topic of Zhao et al.'s review. The issue also contains a discussion of oncolytic viral vectors by Wu et al.

Rapid progress in biomedical research will no doubt unveil more drugable targets and improve drug delivery efficacy. Meanwhile, the emergence of new targets also imposes new challenges for both mechanistic understanding of cell movement and drug delivery. For example, the therapeutic strategy based on stem or progenitor cells to treat myocardial

infarction requires appropriate migration and homing of these cells to the injured tissue (9). How to direct the migration of stem or progenitor cell to the sites of injury requires a thorough understanding of their motility regulators and/or the innovation of stem or progenitor cell delivery mechanism.

Although challenges remain in therapeutic design and drug delivery that specifically target pathological cell movement, the perspective based on the current understanding highlighted in this theme issue offers great optimism for the therapeutic strategies that regulate motility. For example, the EMT or EndoMT and MET or MEndoT events after development are often associated with pathological cell movement and therefore provide theranostic opportunities for malignant and cardiovascular diseases, as discussed by Chua et al. in this issue. Other examples given in this issue include the unique role of tumor-host interaction in tumor cell invasiveness, as highlighted by Palmer et al., and the motility-regulatory role of some cytochrome P450 epoxigenases in tumor progression, as reviewed by Xu et al. Future studies will focus on i) developing the therapeutic targets and biomarkers highly selective to pathological motility, including the evaluation of cell movement as endpoints for clinical treatment and trials, and ii) upgrading the specificity and efficacy of nanomedicine delivery system.

We would like to offer our sincere thanks to all the contributors of this issue. We hope their outstanding contributions provide greater insights into the important role of cell motility in cardiovascular and malignant diseases. We hope this issue provides stimulation for innovative approaches and development of novel therapies by gaining insights into this fascinating field.

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References

1. Thiery JP, Acloque H, Huang RY, Nieto MA. Epithelial-mesenchymal transitions in development and disease. *Cell*. 2009; 139:871–90. [PubMed: 19945376]
2. Visvader JE. Cells of origin in cancer. *Nature*. 2011; 469:314–22. [PubMed: 21248838]
3. Bockhorn M, Jain RK, Munn LL. Active versus passive mechanisms in metastasis: do cancer cells crawl into vessels, or are they pushed? *Lancet Oncol*. 2007; 8:444–8. [PubMed: 17466902]
4. Alix-Panabieres C, Riethdorf S, Pantel K. Circulating tumor cells and bone marrow micrometastasis. *Clin Cancer Res*. 2008; 14:5013–5021. [PubMed: 18698019]
5. Hüsemann Y, Geigl JB, Schubert F, Musiani P, Meyer M, Burghart E, Forni G, Eils R, Fehm T, Riethmüller G, Klein CA. Systemic spread is an early step in breast cancer. *Cancer Cell*. 2008; 13:58–68. [PubMed: 18167340]
6. Condeelis JS, Segall JE. Intravital imaging of cell movement in tumours. *Nat Rev Cancer*. 2003; 3:921–930. [PubMed: 14737122]
7. Smith SC, Theodorescu D. Learning therapeutic lessons from metastasis suppressor proteins. *Nat Rev Cancer*. 2009; 9:253–64. [PubMed: 19242414]
8. Haverslag R, Pasterkamp G, Hoefer IE. Targeting adhesion molecules in cardiovascular disorders. *Cardiovasc Hematol Disord Drug Targets*. 2008; 8:252–60. [PubMed: 19075635]
9. Smart N, Riley PR. The stem cell movement. *Circ Res*. 2008; 102:1155–68. [PubMed: 18497316]