News Release

Title

TRIM27/MRTF-B-dependent integrin β1 expression defines leading cells in cancer cell collectives

Key Points

- ○Invading cancer cell groups establish two different cell types: leading cells (LCs), which lead the group, and following cells (FCs).
- ○TRIM27/MRTF-B complex upregulates integrin β1 expression through repressing microRNA-124 in response to the loss of intercellular adhesion in LCs.
- ○Upregulated integrin β1 is required for collective invasion and metastasis of cancer cells.

Summary

Dr. Takuya Kato (Designated Assistant Professor) and his co-workers led by Prof. Masahide Takahashi (Department of Pathology) in Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, M.D., Ph.D.) found that leading cells (LCs) at the forefront of collectively invading cancer cell group express higher integrinβ1 than following cells (FCs) at the rear. The LC-specific expression of integrin β1 was post-transcriptionally regulated by the TRIM27/MRTF-B complex in response to the loss of intercellular adhesion, thereby regulating the stability and translation of integrin β1 mRNA via microRNA-124 in LCs. Accordingly, depletion of TRIM27 and MRTF-B abrogated the upregulation of integrin β1 in LCs and blocked the invasion of cancer cell groups in vitro and in vivo. These findings revealed that the specific function of LCs was defined by intrinsic mechanisms related to the presence of the cell's free surface, thereby promoting cancer progression.

The paper on the above result was published online in an English journal Cell Reports (Cell Press) on May 1, 2014 (12 pm, EST in USA).

Research Background

Numerous studies have postulated that invasion into the surrounding stroma requires cancer cells with epithelial cell morphology to undergo a phenotypic conversion termed the epithelial-mesenchymal transition (EMT) wherein they lose their intercellular adhesion ability and acquire mesenchymal morphology and increased invasion potential. Although this hypothesis is widely accepted, most pathologists have not observed cells in transition in human cancer tissues, leading some to suggest that the EMT program is activated in cancer cells instantaneously over short periods of time or is observed only in limited contexts.

Instead, rigorous pathological studies have long suggested that cancers form tightly connected groups of cells in order to invade into neighboring tissues, a phenomenon termed collective cell invasion or migration. The observation that grouped cancer cells circulate in the blood stream of cancer patients further suggests that groups of cancer cells may penetrate into the walls of blood or lymphatic vessels. Although collective cell

invasion and migration have attracted much attention in recent years, the underlying mechanisms, which are distinct from single cell invasion/migration, have not been fully resolved.

Research Results

The research group precisely observed the LC-specific expression of integrin β1 in lung cancer tissue. Based on the observation, they sought the molecule which regulates integrin β1 expression in LCs. They found that two transcriptional regulators TRIM27 and MRTF-B upregulate integrin β1in LCs, but not in FCs, through repressing the expression of micrRNA-124, which targets and inhibits the integrin β1 mRNA. In this process, the loss of intercellular adhesion at the free edge of LCs activates a small molecule GTPase RhoA which regulates the function of TRIM27/MRTF-B. In FCs, this mechanism does not work because the cells are surrounded by other cells, which results in differential expression of integrin β1 between LCs and FCs. They further revealed that the increased expression of integrin β1 in LCs is required for collective invasion and metastasis. Present study reveals the mechanism through which LCs, but not FCs, detect the presence of free surface in contact with the space around them and translate this into an LC-specific protein expression pattern, thereby promoting cancer progression.

Research Summary and Future Perspective

In summary, this study provides a novel mechanism of how collectively invading cancer cells establish LCs and FCs and its significance in cancer invasion and metastasis. Because metastasis is generally the cause of cancer-related death, present study may contribute to develop a new anti-cancer therapeutics which improves the survival of patients.

Kato T, Enomoto A, Watanabe T, Haga H, Ishida S, Kondo Y, Furukawa K, Urano T, Mii S, Weng L, Ishida-Takagishi M, Asai M, Asai N, Kaibuchi K, Murakumo Y, Takahashi M. TRIM27/MRTF-B-dependent integrin β1 expression defines leading cells in cancer cell collectives. Cell Reports（To be published on May 1,2014）

Japanese ver.

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