News Release

Title

Akt-Girdin Signaling in Cancer-Associated Fibroblasts Contributes to Tumor Progression

Key Points

- It was revealed that Girdin, an Akt substrate, is expressed and phosphorylated in cancer cells and cancer-associated fibroblasts (CAF) in human breast cancer.
- The growth of transplanted tumor in knock-in mice defective in Girdin phosphorylation decreased compared with that in wild-type mice.
- The ability of tumor progression by CAF deficient for Girdin phosphorylation was decreased compared with wild-type CAF
- It was suggested that the inhibition of Akt signaling in not only cancer cells but also CAF could improve the efficacy of cancer therapy.

Summary

Dr. Masahide Takahashi, Department of pathology, Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, M.D., Ph.D.), and colleagues elucidated one of the important signals in cancer-associated fibroblasts (CAF) to promote tumor growth. This study was reported online March 2th, 2015 in Cancer Research.

In recent years the tumor microenvironment has emerged as an important target for cancer therapy. However, the details of the pathways in the tumor microenvironment that provides crucial oncogenic signals and accelerates tumor growth remain unclear. Here, the investigators reported that Girdin, an Akt substrate that binds the actin cytoskeleton and regulates cell migration, is expressed and phosphorylated in CAF and blood vessels within the tumor microenvironment. They found that allogeneic Lewis lung tumor tissues grown in knock-in mice defective in Akt-mediated Girdin phosphorylation (SA mice) show decreased infiltration of CAF and limited tumor growth, compared with that observed in wild-type (WT) mice. In addition, Lewis tumor tissues displayed limited growth when co-transplanted with CAF from tumor-bearing SA mice vs. CAF from WT mice. Collectively, these findings reveal a role for Akt-mediated Girdin phosphorylation in CAF during tumor progression, highlighting the importance of Akt inhibition in both tumor cells and in other cells that comprise the tumor microenvironments.

Research Background

Tumor cells recruit a diverse array of cell types to their surrounding stroma, including cancer-associated fibroblasts (CAF), endothelial cells (EC) and pericytes that constitute tumor vessels, immune cells such as

tumor-associated macrophages (TAM), and adipocytes, leading to the formation of highly complex neoplastic tissues. In turn, the tumor microenvironment facilitates tumor progression and metastasis by providing a matrix for the integration of intricate networks suitable to maintain and nourish tumor cells, as well as suppress the normal immunological anti-tumor defenses. Previous studies have established that the Akt signaling pathway is critical for the development, progression, and metastasis of malignant tumors. However, the roles of Akt pathway in the tumor microenvironment that provides crucial oncogenic signals and accelerates tumor growth remain unclear.

Research Results

Here, the investigators reported that Girdin, an Akt substrate that binds the actin cytoskeleton and regulates cell migration, is expressed and phosphorylated in CAF and blood vessels within the tumor microenvironment of human breast cancer. They demonstrate that allogeneic Lewis lung tumor tissues grown in knock-in mice defective in Akt-mediated Girdin phosphorylation (SA mice) show decreased infiltration of CAF and limited tumor growth, compared with that observed in wild-type (WT) mice. In contrast to previous studies, we found that Akt-dependent Girdin phosphorylation was not rate limiting in EC. Proliferation and migration of skin fibroblasts from SA mice were impaired compared with WT fibroblasts *in vitro* assay. In addition, Lewis tumor tissues displayed limited growth when co-transplanted with CAF from tumor-bearing SA mice compared with CAF from WT mice.

Research Summary and Future Perspective

Collectively, these findings suggest a novel mechanism whereby Akt signaling is central to both tumor cells and cells that constitute the tumor microenvironment. This study provides a basis for the potential targeting of the Akt-Girdin signaling pathway within the tumor microenvironment, to develop novel therapies against human malignancies.

The authors and title of the paper

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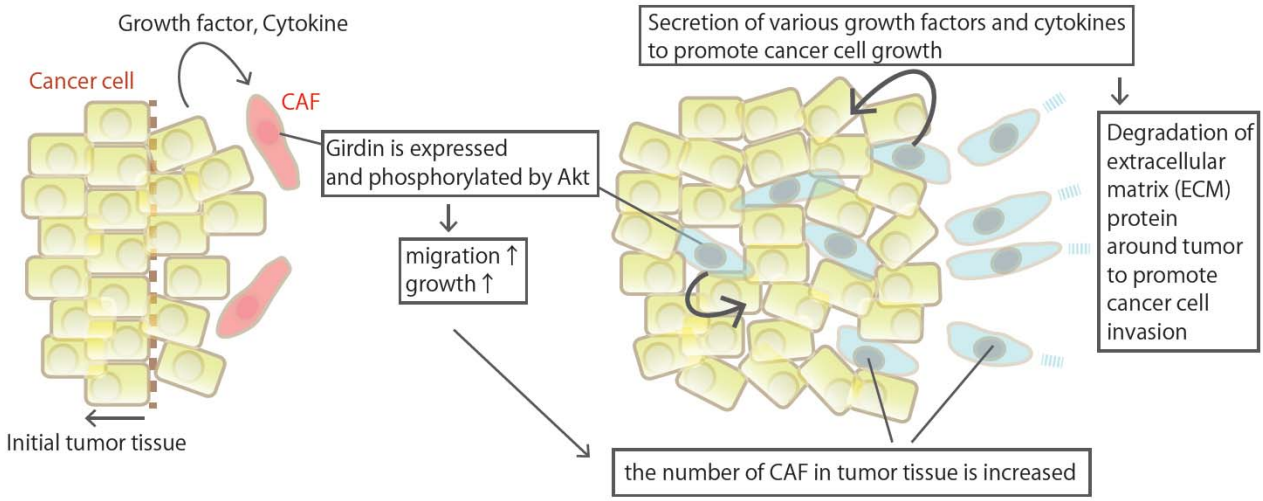

Figure. Roles of Cancer-Associated Fibroblasts in Tumor Progression

Japanese ver.

http://www.med.nagoya-u.ac.jp/medical/dbps_data/_material_/nu_medical/_res/topix/2014/ark-girdin_20150303jp.pdf