Antitumor potential of fibulin-5 in breast cancer cells depends on its RGD cell adhesion motif

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Background/Aims: Different components of the tumor microenvironment can be either tumor-promoting or tumor-suppressive agents depending on factors which are not fully understood. Fibulins are components of the extracellular matrix from different tissues and constitute a clear example of this dual function. In fact, fibulins may either support tumor growth or abolish progression of malignant cells depending on the crosstalk between tumor cells and their surrounding stroma through mechanisms that remain to be elucidated. Among all fibulins, fibulin-5 contains a particular structural hallmark which consists in the presence of a RGD motif within its architecture. Previous reports have highlighted the importance of the interaction of this motif with integrins, and not only in normal functions but also in a tumor context. Methods: Site-Directed Mutagenesis technique was employed to introduce the change RGD to RGE (RGD-to-RGE) within Fbln5 cDNA sequence. Cell proliferation was measured using the MTT assay or by counting Ki-67 positive cell nuclei. Cell adhesion was analysed using culture plates coated with different extracellular matrix components. Cell invasion was evaluated using 24-well Matrigel-coated invasion chambers, and mammosphere formation was monitored using ultralow attachment culture plates. BALB/c mice were employed to induce subcutaneous tumors. Results: The RGD-to-RGE change alters the capacity of breast

cancer cells to adhere to different extracellular matrix proteins as well as to ?v?3 and ?5?1 integrins, and promotes protumor effects using different cell-based assays. Moreover, 4T1 cells, a mouse breast cancer cell line model, shows an increased capacity to generate tumors when exogenously expresses fibulin-5 with a RGD-to-RGE change, and such capacity is similar to that shown for 4T1 cells with an interfered Fbln5 gene. Conclusion: These data highlight the importance of the RGD motif of fibulin-5 to induce antitumor effects and provide new insights into the involvement of fibulins in tumor processes. © 2019 The Author(s).

Breast cancer

Fibulin

RGD motif

Tumor microenvironment

arginylglycylaspartic acid

arginylglycylglutamine

complementary DNA

fibulin 5

scleroprotein

tripeptide

unclassified drug

very late activation antigen 5

vitronectin receptor

arginyl-glycyl-aspartic acid

cadherin

FBLN5 protein, human

oligopeptide

recombinant protein

scleroprotein

vimentin

animal experiment

animal model

antineoplastic activity

Article

breast cancer

breast cancer cell line

carcinogenesis

cell adhesion

cell culture

cell proliferation

cell viability assay

controlled study

DNA sequence

extracellular matrix

Fbln5 gene

gene

human

human cell

male

mouse

MTT assay

nonhuman

priority journal

protein expression

protein function

protein motif

protein protein interaction

site directed mutagenesis

allotransplantation

animal

Bagg albino mouse

biosynthesis

breast tumor

cell motion

drug effect

female

genetics

metabolism

neoplasm

pathology

tumor cell line

Animals

Breast Neoplasms

Cadherins

Cell Adhesion

Cell Line, Tumor

Cell Movement

Cell Proliferation

Extracellular Matrix Proteins

Female

Humans

Male

Mice

Mice, Inbred BALB C

Mutagenesis, Site-Directed

Neoplasms

Oligopeptides

Recombinant Proteins

Transplantation, Homologous

Vimentin