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Breast carcinoma metastasis suppressor gene 1 (BRMS1): Update on its role as the suppressor of cancer metastases in the context of combinatorial cancer treatment

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Background: BRMS1 (Breast Cancer Metastasis Suppressor-1) protein was discovered over a decade ago as a potential tumor suppressor gene. Our review summarizes the recent findings about the structure of BRMS1, mechanisms of its action and the role of BRMS1 in the cancer progression. In addition, I would like to discuss the BRMS1 findings in a broader context. Combinatorial treatment of breast cancer with the joined forces of chemotherapy, adjuvant therapy, cytotoxic agents and radiation has had a great impact on the prolonged survival of breast cancer patients. Metastasis remains however the major reason behind the mortality rate in this group of patients and as such requires more attention in understanding the potential influence of other parallel pharmaceutical treatments.

Objectives: The aim of my presentation will be to summarize the recent findings regarding the effect of BRMS1 protein on the suppression of cancer metastasis as well as to explore the correlation between the activity of BRMS1 protein, growth factors (TGF-β and EGF), antidepressants (fluoxetine and amitriptyline) and the stimulation of cell survival and migration of breast cancer.cells in a combinatorial cancer treatment.

Results: As a suppressor of metastasis, BRMS1 has demonstrated a variety of ways to act on the cell functions, such as cell migration, invasiveness, angiogenesis, cell survival, cytoskeleton rearrangements, cell adhesion, and immune recognition. This variety of effects is a likely reason behind the robustness of anti-metastatic influence of BRMS1. Intracellular signaling mechanisms employed by BRMS1 include regulation of transcription, EGF/HER2 signaling, and expression of NF-kB, fascin, osteopontin, and IL-6. Recently reported clinical studies confirm that BRMS1 can indeed be used as a prognostic marker. Approaches to employ BRMS1 in a development of anti-cancer treatment have also been made. The combinatorial influence of growth factors and antidepressants showed a dynamic modulation depending 2 on the presence of BRMS1 protein. It indicates the existence of a correlation between BRMS1, TGF-β, EGF, fluoxetine and amitriptyline. Furthermore, the effect of antidepressants differed depending on the kind of parallel treatments and therefore underlined the significance of drug-drug interactions. Antidepressant amitriptyline strongly promoted colony formation in MDA-MB-231-pMEP4 cell line, which was observed in both membrane migration assay and clonogenic assay. The same treatment resulted in a complete inhibition for MDA-MB-231-pMEP-BRMS1 cell line. Although the study requires to be confirmed by larger number of experiments, it may suggest that breast cancer patients taking amitriptyline (while not expressing BRMS1 protein) are exposed to increased risk of metastasis. On the other hand, for breast cancer patients who express BRMS1 protein and are treated with amitriptyline, it may imply an outstanding inhibiting effect of amitrypryline treatment on metastasis. Moreover, BRMS1 proved to have an impact on fluoxetine activity by inhibiting the stimulating effect of fluoxetine on the treatments with TGF-β, which were earlier observed in MDA-MB-231-pMEP4 cell line. In contact inhibition assay the stimulation of senescent cells by BRMS1 may suggest the role of BRMS1 in the inhibition of uncontrolled cancer.cell.proliferation. Conclusions: The studies reviewed here with respect to BRMS1 structure, cellular effects, intracellular signaling, and clinical value consolidate the importance of BRMS1 in the development of metastasis. In addition, the results of our study imply a significant correlation between BRMS1 protein, growth factors and antidepressants. A strong, opposite impact of amitriptyline on colony formation in both BRMS1-expressing and non-expressing cell lines requires a further investigation of the mechanism of interactions between BRMS1 and the treatment agents used in the study. It is advised in order to improve the outcome of the cancer treatment as well as the cancer related depression treatment. Furthermore, the results indicate that the future cancer treatment needs to consider not only drug-drug interactions but also a cross-talk between the drugs and the proteins involved in the cell growth and metastasis.

Biography

Two Master of Science degrees (Medical Physics, AGH, Krakow, Polen and Molecular Biotechnology, KTH, Stockholm, Sweden). Both of my theses were performed and defended with highest grades at Karolinska Institute in Stockholm, Sweden. The results of my Master of Science thesis in Molecular Biotechnology turned out to be so interesting that I had a pleasure to present them at Personalized Cancer Care Symposium in Oslo (Norway) in 2012. My supervisor at Karolinska Institute, Serhiy Souchelnytskiy, saw so much scientific potential in me during my work at his lab that he invited me to write a review which was published in Cancer and Metastasis Reviews Journal and which was met with a worldwide interest and many invitations to conferences. The findings of my review as well as my own personal experimental results are so interesting and crucial for the development of combinatorial cancer treatment that I hope I will have a pleasure to present them at your esteemed congress in Philadelphia in December and inspire a positive development in combinatorial cancer therapy.

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