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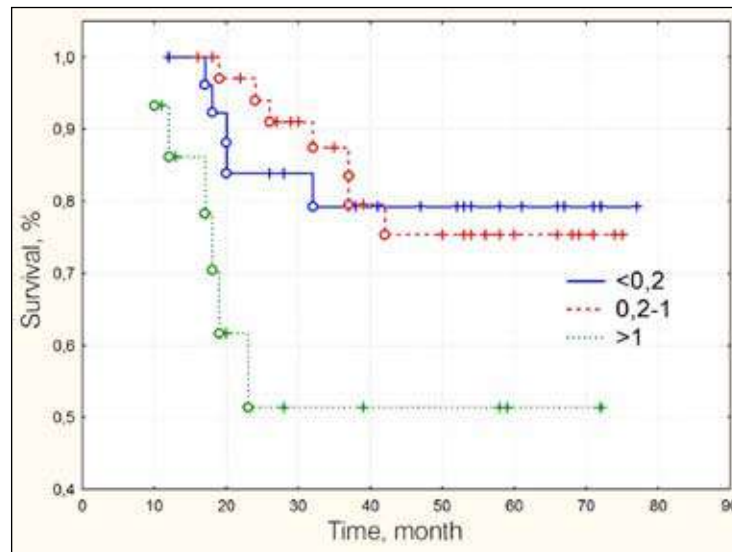


Figure 1. The parameters of the metastasis-free survival of breast cancer patients, depending on the expression level of *BRCA1* (log-rank test $p < 0.05$)

There was a statistically significant increase in metastasis-free survival values with a *BRCA1* expression level of less than 0.2 ($p=0.05$) and 0.2-1 ($p=0.01$) as compared to a *BRCA1* value of more than 1.

Thus, the association of *BRCA1* gene expression in breast tumor with the prognosis of the disease was demonstrated. Based on the data obtained, it can be assumed that the expression of *BRCA1* may also be a marker of the effectiveness of treatment of breast cancer patients, but this requires further study.

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UP-REGULATION OF FLOTILLINS, NEW MARKER OF METASTATIC DEVELOPMENT, INDUCES CELL INVASION AND METASTATIC DEVELOPMENT

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Flotillin 1 and 2 are two ubiquitous, highly conserved and related proteins present in many cellular membrane compartments. They exist as hetero-tetramers associated with specific caveolin-independent membrane microdomains rich in cholesterol and glycosphingolipids. Flotillin hetero-tetramers assemble in large oligomers to form molecular membrane scaffolds known to participate in membrane proteins clustering [1]. When overexpressed, as it occurs in many invasive carcinoma and sarcoma, they induce the formation of plasma membrane invaginations and of intracellular vesicles and modify the trafficking of several cargos; promoting the Upregulated Flotillin-Induced Trafficking (UFIT) pathway [2-3].

Flotillin overexpression is detected in many invasive carcinoma and sarcoma and is a marker of poor prognosis associated with a higher metastatic risk [4-8]. How flotillins participate in the acquisition of invasive and metastatic properties remains to be determined.

Our study aims at identifying how the UFIT pathway influences the membrane remodeling and modifies the trafficking of cargo leading to the acquisition of invasive properties.

We show that flotillins downregulation in invasive cancer cells dramatically inhibit their invasive properties as monitored *in vitro* using a 3D-collagen invasion assay and *in vivo* using zebrafish xenografts. Reciprocally, ectopic up-regulation of flotillins in non-tumoral cells is sufficient to induce their invasive behavior *in vitro* and *in vivo*. We show that flotillins are critical regulators of the trafficking of several cargo amongst them MT1-MMP, a key metalloproteinase responsible for the proteolytic activity of invadopodia [9].

Keywords: flotillins, cancer marker, metastasis, cell invasion.

REFERENCES

1. Bodin S., Planchon D., Rios Morris E., Comunale F., Gauthier-Rouviere C. Flotillins in intercellular adhesion - from cellular physiology to human diseases. *J Cell Sci.* 2014 Dec 15; 127(Pt 24): 5139-47. doi: 10.1242/jcs.159764.
2. Frick M., Bright N.A., Riento K., Bray A., Merrified C., Nichols B.J. Coassembly of flotillins induces formation of membrane microdomains, membrane curvature, and vesicle budding. *Curr Biol* 2007, 17:1151–1156. doi: 10.1016/j.cub.2007.05.078.
3. Glebov O.O., Bright N.A., Nichols B.J. Flotillin-1 defines a clathrin-independent endocytic pathway in mammalian cells. *Nat Cell Biol.* 2006; 8: 46–54. doi: 10.1038/ncb1342.
4. Cao S., Cui Y., Xiao H., Mai M., Wang C., Xie S., Yang J., Wu S., Li J., Song L., Guo X., Lin C. Upregulation of flotillin-1 promotes invasion and metastasis by activating TGF- β signaling in nasopharyngeal carcinoma. *Oncotarget.* 2016 Jan 26; 7(4): 4252-64. doi: 10.18632/oncotarget.6483.
5. Koh M., Yong H.Y., Kim E.S., Son H., Jeon Y.R., Hwang J.S., Kim M.O., Cha Y., Choi W.S., Noh D.Y., Lee K.M., Kim K.B., Lee J.S., Kim H.J., Kim H., Kim H.H., Kim E.J., Park S.Y., Kim H.S., Moon W.K., Choi Kim H.R., Moon A. A novel role for flotillin-1 in H-Ras-regulated breast cancer aggressiveness: Flotillin-1 is Important for Breast Cancer Aggressiveness. *Int J Cancer.* 2016 Mar 1; 138(5): 1232-45. doi: 10.1002/ijc.29869.
6. Liu Y., Lin L., Huang Z., Ji B., Mei S., Lin Y., Shen Z. High expression of flotillin-2 is associated with poor clinical survival in cervical carcinoma. *Int J Clin Exp Pathol.* 2015; 8: 622–628.
7. Li H., Wang R.-M., Liu S.-G., Zhang J.-P., Luo J.-Y., Zhang B.-J., Zhang X.-G. Abnormal expression of FLOT1 correlates with tumor progression and poor survival in patients with non-small cell lung cancer. *Tumour Biol.* 2014 Apr; 35(4): 3311-5. doi: 10.1007/s13277-013-1434-3.
8. Wang X., Yang Q., Guo L., Li X.H., Zhao X.H., Song L.B., Lin H.X. Flotillin-2 is associated with breast cancer progression and poor survival outcomes. *J Transl Med.* 2013 Aug 15; 11: 190. doi: 10.1186/1479-5876-11-190.
9. Castro-Castro A., Marchesin V., Monteiro P., Lodillinsky C., Rosse C., Chavrier P. Cellular and Molecular Mechanisms of MT1-MMP-Dependent Cancer Cell Invasion. *Annu Rev Cell Dev Biol.* 2016 Oct 6; 32: 555-576. doi: 10.1146/annurev-cellbio-111315-125227.

CIRCULATING DNA-MARKERS IN LUNG CANCER: CHANGES IN RETROTRANSPOSONS METHYLATION STATUS IN RESPONSE THERAPY AND DURING THE POST-TREATMENT FOLLOW-UP

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Background

Malignant cell transformation is accompanied by two processes of DNA methylation changes: hypermethylation in CpG islands of tumor suppressor genes and global hypomethylation in repetitive DNA sequences (retrotransposons) [1, 2]. The composition of circulating DNA (cirDNA) from plasma and cell-surface-bound cirDNA (csb-cirDNA) was shown earlier to be altered in the blood of cancer patients due to accumulation of tumor-specific aberrantly methylated DNA fragments, which are currently considered valuable cancer markers [3, 4].

Material and Methods

The present study compared LINE-1 retrotransposon methylation patterns in free-cirDNA and csb-cirDNA from healthy subjects (n=33) and lung cancer (LC) (n=32) patients, and also from