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Through which pathway does trastuzumab and miR-122-5p combinatorial administration lead breast cancer cells to apoptosis: Intrinsic or extrinsic pathway?

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Statement of the Problem: In most of breast cancer cells, HER2 receptors are known to be cleaved by an ectodomain sheddase, ADAM10, to liberate HER2 extracellular domain (ECD). This provides ligand-independent growth to breast cancer cells and trastuzumab, anti-HER2 agent, cannot inactivate HER2 by binding ECD portion of it. In our previous studies, we found that miR-122-5p, miRNA targeting ADAM10, and trastuzumab combinatorial administration to HER2-positive breast cancer cell line, SKBR3, increases the efficiency of trastuzumab by leading SKBR3 cells to apoptosis more through blocking the sheddase activity of ADAM10 on HER2. The aim of this study is to display that miR-122-5p, together with trastuzumab, leads SKBR3 cells apoptosis by which pathway: intrinsic or extrinsic.

Methodology & Theoretical Orientation: SKBR3 cells were first transfected with the miR-122-5p mimic for 48 hours. Then, 0.5 μM trastuzumab was applied to miR-122-5p-transfected SKBR3 cells and non-transfected SKBR3 cells for 24 hours. Next, the expression levels of CASP3, *CASP8* and *CASP9* genes, which are key molecules in apoptotic pathway, were examined by real-time PCR.

Findings: Expression levels of *CASP3* and *CASP8*, but not *CASP9*, increased significantly in miR-122-5p-transfected Trastuzumab-administered SKBR3 cells when compared to non-miR-122-5p transfected Trastuzumab-administered SKBR3 cells. A significant increase in the expression level of *CASP8* with *CASP3* showed apoptosis to be activated via extrinsic pathway (instead of the mitochondrial intrinsic pathway regulated by *CASP9*) with the effect of miR-122-5p in trastuzumab-administered SKBR3 cells.

Conclusion & Significance: Consequently, the apoptosis enhancing effect of trastuzumab and miR-122-5p combinatorial administration through extrinsic pathway may be presented as a new treatment option for HER2+ breast cancer.

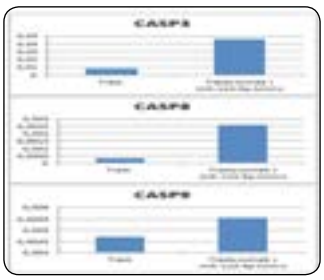

Figure 1: Comparison of expression levels of *CASP3, 8, 9* genes between SKBR3 cells administered with trastuzumab and trastuzumab + miR-122-5p-mimic.

Recent Publications:

1. Ergun S, et al. (2014) Expression patterns of miR-221 and its target caspase-3 in different cancer cell lines. Mol Biol Rep. 41:5877–5881.
2. Wang B, et al. (2012) MiR-122 inhibits cell proliferation and tumorigenesis of breast cancer by targeting IGF1R. PLoS One 7(10):e47053.
3. Pollack M and Leeuwenburgh C (2001) Apoptosis and aging: role of the mitochondria. J Gerontol A Biol Sci Med Sci. 56(11):B475–B482.

Biography

Sercan Ergun is working as Teaching Assistant in Ordu University and is about to finish his PhD in Department of Medical Biology and Genetics of Ondokuz Mayıs University. He was included as Researcher in a team studying briefly epigenetic changes in disease mechanisms of different types of cancers, including oncogenic/tumor suppressor gene and miRNA expression level changes, cell death mechanism analysis, development of some cancer therapy agents' efficiencies via miRNAs. Now, he is part of a team studying *in silico* miRNA and ceRNA analysis, miRNA heterogenetiy, piRNA expression changes in different cancer types, especially urological cancers. He has many published many articles related to these studies. He and his team have conducted many studies on different diseases other than cancer, like Glanzmann's thrombasthenia, hemophagocytic lymphohistiocytosis, immune thrombocytopenic purpura, familial mediterranean fever, βeta (β)-thalassemia, secondary hyperparathyroidism and he has many other articles on them.

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