Inhibition of RAS-signaling by Bacillus pumilus RNase binase

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RAS proteins play a crucial role in stimulation of specific signaling pathways that govern diverse cellular processes like cell growth, proliferation, differentiation, motility, endocytosis and apoptosis. Due to the key function of RAS proteins in all these processes these activities lead during transformation towards cells malignization. Oncogenic mutations in the RAS genes (HRAS, KRAS and NRAS) are present in approximately 30% of all human cancers and up to 90% in certain types of cancer. So Oncogenic RAS proteins are promising targets for newly developed antineoplastic agents.

We have shown by co-immunoprecipitation assay that secreted Bacillus pumilus RNase binase with established earlier antitumor activity is able to interact directly with the $KRAS^{G12C}$ mutant protein in $KRAS^{G12D}$-transfected MLE-12 cells. By molecular docking analysis using three-dimensional structures of binase and $KRAS^{G12C}$ mutant protein deposited in the Protein Data Bank a model for the these proteins interaction was created and the hypothesis that binase interacts with KRAS like a GTPase-activating protein was confirmed. We have demonstrated that binase inhibits the MAPK/ERK signaling pathway and disrupts SOS1/KRAS protein interaction resulting in a viability decreasing and reducing of cells' migration.

Despite the established RAS proteins' properties to be one of the most important molecular targets of binase, in further studies we have shown RNase's cytotoxisity to cancer cells with normal RAS form. Using MCF-7, ZR-75-1, BT-20, HBL-100 breast cancer cells we revealed that binase induces apotosis of cells with activated PI3K/AKT pathway also involved in RAS-signaling system. Remarkable, binase inhibits proliferation and induces apoptosis of triple negative breast cancer cells BT-20. This fact supports the concept of microbial RNase perspective use as an agent against TNBC, which usually does not respond to conventional therapeutics.

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