A noval PKC-η inhibitory peptide as treatment for TNBC & Leukemia

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Technology

Prof. Livne in collaboration with Prof. Yeger-Lotem identified new target for treatment of triple negative breast cancer (TNBC) and leukemia, and developed modified peptide with increased stability and potency as therapeutic agent. Approximately 40% of human messenger RNAs (mRNAs) contain upstream open reading frames (uORFs) in their 5' untranslated regions. Some of these uORF sequences, thought to attenuate scanning ribosomes or lead to mRNA degradation, were recently shown to be translated, although the function of the encoded peptides remains unknown. Here, the researchers showed a uORF-encoded peptide that exhibits kinase inhibitory functions. This uORF, upstream of the protein kinase C-eta (PKC-η) main ORF, encodes a peptide (uPEP2) containing the typical PKC pseudosubstrate motif present in all PKCs that autoinhibits their kinase activity. They demostarted that uPEP2 directly binds to and selectively inhibits the catalytic activity of novel PKCs but not of classical or atypical PKCs. The endogenous deletion of uORF2 or its overexpression in MCF-7 cells revealed that the endogenously translated uPEP2 reduces the protein levels of PKC-η and other novel PKCs and restricts cell proliferation. Functionally, treatment of triple negative breast cancer cells with uPEP2 having myristoyl group at its N terminal to enable cell penetration, diminished cell survival and their migration and synergized with chemotherapy by interfering with the response to DNA damage. uPEP2 also significantly reduced the viability of leukemia cells. Furthermore, in a xenograft of MDA-MB-231 breast cancer tumor in mice models, uPEP2 suppressed tumor progression, invasion, and metastasis. Tumor histology showed reduced proliferation, enhanced cell death, and lower protein expression levels of novel PKCs along with diminished phosphorylation of PKC substrates. The researchers demonstrates that uORFs may encode biologically active peptides beyond their role as translation regulators of their downstream ORFs. Modified peptide with better potency, better stability and capability to penetrate the cell that acts as kinase inhibitor was shown to be a great candidate for breast cancer therapy.

Application

Drug treatment for TNBC and leukemia. As single therapy or as adjuvant therapy.

Advantages

- New target - uORFs
- Selective inhibition of novel PKCs and not for classical or atypical PKCs
- The treatment is based on a modified naturally occurring peptide therefore considered to have safier profile
- The compound selectively reduces viability, proliferation, and cell migration of only cancer cells but not healthy cells.

Patent

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