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Targeting the nuclear translocation of MAPKs as a novel anti-inflammatory and anti-cancer therapy

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A hallmark of MAPK signaling is their nuclear translocation upon stimulation, which is necessary for their physiological/pathological functions. We have identified two novel, distinct, regulated nuclear translocation mechanisms for ERK1/2 and JNK/p38, of which we made use of as a promising therapeutic approach. We developed a myristoylated, NTS-derived phosphomimetic peptide (EPE peptide), which blocked ERK1/2 nuclear translocation by inhibiting its interaction with importin7 (Imp7). In culture, we showed that the EPE peptide induced apoptosis of melanoma cells, inhibited the proliferation of other cancer cells but had no effect on immortalized cells. In xenograft models, the peptide was significantly more effective than PLX4032, a selective potent BRAF inhibitor, in preventing tumor recurrence of treatment-eradicated melanoma xenografts. We also developed additional p38-derived myristoylated peptide, termed PERY peptide, which prevented JNK1/2 and p38α/β nuclear translocation. When tested in a model of inflammation associated DSS-induced acute colitis, the PERY peptide significantly reduced inflammation and intestinal damage. Using the model of a combined single dose of the carcinogen AOM with repetitive cycles of DSS in order to induce tumorigenesis, we showed that systemic treatment with the PERY peptide significantly prevented colon cancer. Treatment with the PERY peptide significantly reduced tumor load and maintained healthier colon histology, even better than colon of mice treated with the commercial p38 MAPK inhibitor, SB203580. Both the cancer and inflammatory models support the use of nuclear translocation of MAPKs as a novel drug target for signaling related diseases.

Biography

Rony Seger is a Professor and Department Head in the Department of Biological Regulation, the Weizmann Institute of Science in Israel. He has completed his MSc and PhD at the Weizmann Institute and Postdoctoral studies in the group of Edwin G. Krebs, Nobel Laureate, identifying and cloning MEK1. He continues to work on MAPKs and is currently interested mainly in the regulation of sub-cellular localization of MAPK components, in particular their mechanism of nuclear translocation. He has published over 200 papers in leading journals, supervised more than 70 research students and post-doctoral fellows and received many prizes and awards..

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