Treating Cancer by Inhibiting Nuclear Entry of MAPK Cascade Proteins

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Overview

Inhibition of Nuclear Entry of MAPK Cascade Proteins as a Novel Mechanism for Treating Cancer

Background and Unmet Need

ERK is a major signaling molecule, which plays a driving role in various pathologies, particularly cancer. When not activated ERK is localized to the cytoplasm. Upon activation ERK binds to Importin7 (Imp7) and is translocated to the nucleus, where it elicits transcription of numerous genes related to pro-cancerous activities such as proliferation. However, anti-ERK drugs have had limited success in only certain cancer types, and development of drug resistance is a common phenomenon among patients. Anti-ERK drug resistance is usually attributed to the inhibition of the ERK-dependent negative feedback loop, which activates alternative signaling mechanisms. These mechanisms circumvent the ERK cascade, rendering the drugs ineffective.

The research group of Prof. Seger developed a peptide, which inhibits ERK without provoking the typical anti-ERK resistance mentioned above. The peptide achieves that by inhibiting the translocation of ERK to the nucleus in a manner that does not affect the negative feedback loop. This peptide has the potential to treat ERK-related diseases and cancer without inducing drug resistance, as a single therapy or in a combination with standard of care therapies. The group has also developed a small molecule that mimics the mechanism of the peptide, which holds a great promise due to its novel mechanism of action and superiority from the drugability perspective over the administration and use of peptides.

Technology Essence

The peptide interferes with the binding of ERK and Imp7 via the nuclear translocation signal (NTS). If the ERK-Imp7 complex is not properly assembled, ERK is not translocated to the nucleus and therefore cannot induce gene expression and further proliferation. The peptide was tested both in vitro and in vivo in various cancers (for example melanoma, breast and colon) and was shown to reduce proliferation and tumor volume.

Applications and Advantages

- Variety of indications – can be used for many pathologies that require ERK silencing.
- Lack of resistance – does not provoke the ERK negative feedback loop, which contributes to drug resistance.

- Novel – inhibits ERK translocation to the nucleus rather than inhibiting general ERK function.
- Small molecule in development to mimic peptide

Patent Status

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