Exploration for Medicinal Leads Using Nuclear Transport Inhibitors for Nuclear Export Signal (NES) Contained Proteins as Scaffolds

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Recently, some proteins with nuclear export signals (NES) were shown to be exported from nucleus to cytoplasm by the receptor, CRM1. So far representative NES-contained proteins such as MEK and Rev have been elucidated. The former is concerned with proliferation of various tumor cells, the latter is required by replication of HIV-1 virus. In addition, nuclear transport inhibitors for NES-contained proteins were shown to suppress proliferation of the tumor cells and HIV-1 virus potently.

In this context, we were engaged in search for new inhibitors by the assay using NLS-GFP-NES transformed yeast to disclose 1'-acetoxychavicol acetate (ACA) and valtrate from medicinal plants. Subsequently, the two principles were exhibited to inhibit nuclear transport of NES-contained proteins through NES-antagonistic mode. Furthermore, the genuine active species due to ACA and the model structure of CRM1 were established by biological potency of various synthesized analogs. By ingenious use of the active species and the model structure, new medicinal leads with more potent activity than ACA were rationally furnished.

On the other hand, we constructed the bioassay to search for unprecedented NES-nonantagonistic MEK transport inhibitors to find out peumusolide A from the South American medicinal plant. Additionally, a synthesized analog with the same biological score as peumusolide A was disclosed by establishment of practical synthetic protocol.