A platform for screening potential Ras inhibitors

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Keywords: Cancer, Ras proteins, Ras inhibitors

Abstract:

Ras are small G proteins that regulate important biological processes including cell proliferation, differentiation, survival and metabolism. Ras proteins cycle between an active GTP-bound and an inactive GDP-bound state. Gain of function mutations of Ras genes have been found in almost 30% of human tumors, in the totality of pancreatic cancer, and in up to 50% of colorectal cancer. The oncogenic mutations mainly occur in codons 12, 13, and 61, critical for the nucleotide-binding and protein function. Despite 30 years of research, promising therapeutic strategies have been developed only against the KRasG12C mutant.

The aim of this study is to develop a platform for the screening and identification of Ras inhibitors, possibly selective for G13D or G12V mutants, from synthetic and natural compounds, even in a complex source such as plant extracts (Tisi et al., 2020, Tisi et al. 2021).

The platform includes purified oncoproteins on which to test the binding and inhibitory action of the screened molecules, and advanced cellular models over-expressing the oncogenic mutants on which to evaluate the antiproliferative effect associated with the attenuation of the Ras signaling.

This platform has been successfully used to identify potential Ras inhibitors in *Vigna unguiculata* leaf extract (Prof. Labra) and Cocoa bean extract (Dr. Campone). Both extracts showed a dose-dependent capacity to reduce the Ras-bound nucleotide exchange *in vitro* and the cell viability of Ras-dependent cancer cells.

The analysis of the Ras-binding properties of rosmarinic acid (Prof. Airoldi) and a library of commercial compounds selected by A.I. virtual screening (Atomwise-San Francisco, USA) is also ongoing.

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