A platform for screening potential Ras inhibitors

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Abstract:
Ras are eukaryotic small guanine nucleotide-binding (G) proteins that regulate critical cellular processes, such as proliferation, survival, growth, differentiation, motility, and metabolism in response to specific stimuli [1]. Deregulation of Ras activity, in particular of KRas isoform, has a driving role in human developmental pathologies known as RASophaties and in nearly one-third of human cancers. Ras pathological variants are important clinical targets and are suitable for developing pharmacological inhibitors [2]. Different synthetic and natural compounds with Ras inhibitory properties have been identified [3-5]. We generated a platform for the screening and identification of Ras inhibitors, possibly selective for G13D or G12V oncogenic mutants, including digital and experimental models on which to evaluate the effect of synthetic and natural compounds, even in a complex source, such as plant extracts. The digital models include three-dimensional structures of Ras proteins already available in the Protein Data Bank (PDB) on which to test, by molecular docking, the structural complementarity between the screened compounds and the Ras pockets important for the protein function. The experimental models, on the other hand, include (i) purified proteins, on which to test the in vitro binding (by NMR and Biacore Surface Plasmon Resonance) and inhibitory action of the screened molecules (biochemical functional assays), and (ii) Ras-dependent breast and colorectal cancer cellular models where to evaluate the antiproliferative effect associated with the attenuation of Ras signalling (growth kinetics, cell viability assays, etc.). Preliminary data, using this platform, indicate that rosemary, sage and *Vigna unguiculata* leaves contain interesting active compounds interfering with Ras signalling, whose molecular mechanisms are under investigation.

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