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Review

Synthesis of Ras proteins and their application in biofunctional studies

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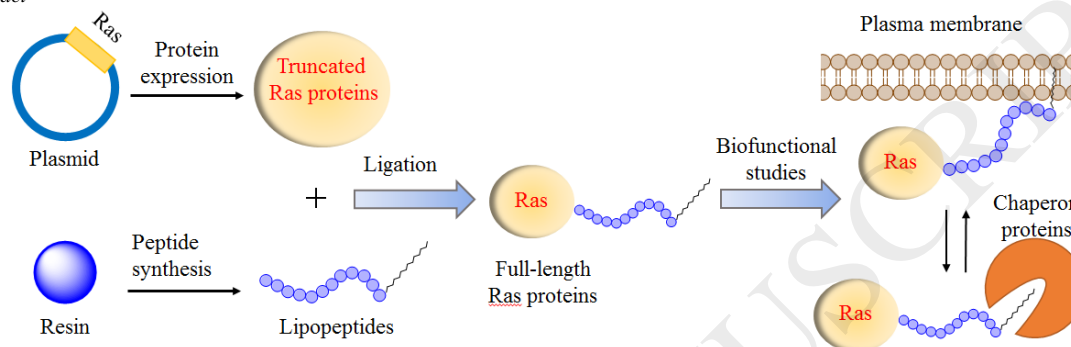
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Graphical abstract



We summarized the developed strategies including chemical total synthesis, biosynthesis and semi-synthesis for producing Ras proteins with modification and their application in biological studies.

ABSTRACT

Approximately 30% of human cancers are associated with *RAS* mutation. Ras proteins on the plasma membrane regulate a plenty of important cellular processes. The post-translational modifications (PTMs) of Ras proteins like lipidation and methylation are crucial for their correct cellular localization and biological function. Hence, obtaining Ras proteins with different kinds of modifications is the necessary prerequisite to investigate their biological properties at molecular level. In this review, we mainly summarize the developed strategies including chemical total synthesis, biosynthesis and semi-synthesis for producing Ras proteins with modifications and their application in biological studies.

Keywords:- Ras Lipopeptides Semi-synthesis Multi-PTMs Biophysical function

1. Introduction

Ras proteins function as molecular switches in some important cellular signaling pathways through cycling between active GTP-bound state and inactive GDP-bound state, which regulate plenty of cell processes, including cell survival, proliferation, differentiation, apoptosis and cytoskeletal dynamics [1]. The genetic mutations of *RAS* genes that persistently activate downstream signaling pathways, can cause cancers. About 30% of human cancers are associated with *RAS* mutations [2]. In order to trigger the downstream signaling, Ras proteins must bind to the inner face of plasma membrane, which requires the lipid and methyl modifications at the C-terminal tail of proteins. These protein post-translational modifications (PTMs) play a key role in regulating membrane association and cellular process of Ras proteins, like trafficking process and protein-protein interactions [3]. However, lacking appropriate protein tools with PTMs had been a big hindrance to the biofunctional studies of Ras proteins. In recent years, the chemical biology approaches, like protein chemical synthesis and semi-synthesis, have experienced huge advances and brought great chances to obtain Ras proteins with multi-modifications. These synthesized Ras proteins largely facilitate the related functional research. Thus, this mini-review mainly summarizes recent strategies for the synthesis of Ras proteins and their applications in biofunctional studies.

2. Ras proteins

Ras proteins are guanine nucleotide-bound proteins (G proteins), which are encoded by *RAS* genes. *RAS* subfamily contains three genes (*NRAS*, *HRAS*, and *KRAS*), which can translate into four protein isoforms: N-Ras, H-Ras, K-Ras4A and K-Ras4B [4]. All of Ras proteins are composed of two parts: one is the G domain (the first 165 amino acids), which is highly conserved; the other is the hypervariable region (HVR), which contains approximately 20 amino acids (Fig. 1). Ras proteins are under a dynamic equilibrium between ‘on’ and ‘off’ conformations which are conferred by GTP and GDP exchanging. Normally, the active GTP-bound state can be

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