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Review

Interactions of Ras proteins with the plasma membrane and their roles in signaling

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Abstract

The complex dynamic structure of the plasma membrane plays critical roles in cellular signaling; interactions with the membrane lipid milieu, spatial segregation within and between cellular membranes and/or targeting to specific membrane-associated scaffolds are intimately involved in many signal transduction pathways. In this review, we focus on the membrane interactions of Ras proteins. These small GTPases play central roles in the regulation of cell growth and proliferation, and their excessive activation is commonly encountered in human tumors. Ras proteins associate with the membrane continuously via C-terminal lipidation and additional interactions in both their inactive and active forms; this association, as well as the targeting of specific Ras isoforms to plasma membrane microdomains and to intracellular organelles, have recently been implicated in Ras signaling and oncogenic potential. We discuss biochemical and biophysical evidence for the roles of specific domains of Ras proteins in mediating their association with the plasma membrane, and consider the potential effects of lateral segregation and interactions with membrane-associated protein assemblies on the signaling outcomes.

Keywords: Ras; Membrane association; FRAP; Lateral domains; Membrane-cytoplasm exchange; Transbilayer signaling

Contents

1. Introduction

Many cellular responses require the tethering of signaling proteins to the membrane. The biophysical nature of this association, which depends on interactions between several cellular constituents including lipids, membrane proteins, protein–lipid assemblies/scaffolds and cytoskeletal elements [1–4], is inseparable from the biological regulation of their

Abbreviations: D, lateral diffusion coefficient; DMPC, 1,2-dimyristoylglycero-3-phosphocholine; EM, electron microscopy; FRAP, fluorescence recovery after photobleaching; GFP, green fluorescent protein; GPI, glycosylphosphatidylinositol; HA, influenza hemagglutinin; HVR, hypervariable region; PLCγ, phospholipase Cγ; wt, wild-type.

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responses. In the absence of a higher level of organization and compartmentalization endowed by the plasma membrane, signaling specificity and fidelity would be largely hampered. Signaling proteins interacting with the internal face of the plasma membrane can be divided into several classes. One class, which includes many of the small GTPases, exhibits continuous dynamic interactions with the internal leaflet of the plasma membrane by specific lipid modifications and/or polybasic clusters. We focus here on the small GTPases H-, K- and N-Ras, which are essential components of signaling cascades that regulate cell growth, differentiation and apoptosis [5–8].

Ras GTPases constitute molecular switches anchored in the internal leaflet of the plasma membrane, regulating multiple signaling pathways; the major Ras-activated effectors in the different pathways are Raf kinases (the Mek/Erk pathway), phosphatidylinositol 3-kinases (PI3K) and Ral guanine nucleotide exchange factors (Ral-GEF) [5–10]. Ras proteins alternate between a GDP-bound, inactive form and a GTP-loaded, activated conformation [11], and control cell growth, proliferation, apoptosis and differentiation [6–8,12–16]. Oncogenic Ras can transform cells both in vitro and in vivo [15], and was shown to contribute to neoplastic processes by overactivation of several pathways [6,9,10,17]; the importance of specific Ras-activated pathways to transformation appears to depend on the species [18,19].

There are four mammalian Ras proteins, encoded by three *ras* genes: H-Ras, N-Ras, K-Ras4A and K-Ras4B. The latter of the last two is the more abundant in mammalian cells, and will be referred to hereafter as K-Ras, The Ras isoforms are highly homologous; their G-domain (residues 1–165; Fig. 1), which binds guanine nucleotides and is required for the switch function and for effector binding, is nearly identical. On the other hand, their C-termini (last 24–25 amino acids), termed "the hypervariable region" (HVR), are highly varied between

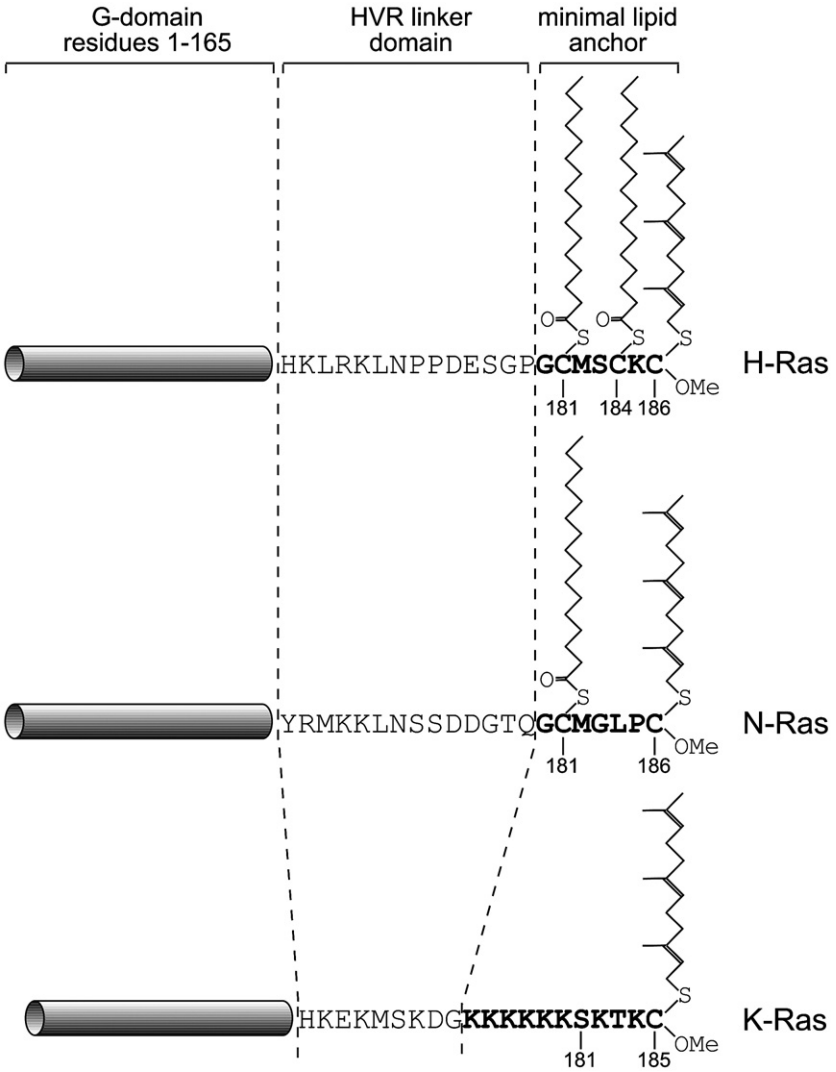

Fig. 1. Domain structure of Ras isoforms. The fully processed forms of the proteins are shown. The minimal lipid anchor (bold) is at the C-termini, containing a farnesyl moiety (all Ras isoforms), one (N-Ras) or two (H-Ras) palmitoyl moieties, or a six-lysine polybasic cluster (K-Ras). The numbers of amino acid residues that undergo specific modifications are depicted below the relevant residues. The lipid anchor is connected to the HVR linker domain, and together they comprise the complete HVR domain. The HVR linker is preceded by the G-domain (residues 1–165), which is highly homologous in all Ras isoforms.