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Ras Signaling Pathway, Historical View

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Abstract

It is increasingly clear that the three RAS genes, N-. H- and K-RAS, encode 21 kDa proteins which act as intracellular switches, play a signal transduction pathway in controlling cell growth and differentiation. The three genes are highly homologous, yet recent evidence suggests they may have distinct functions in different cell types and have a central role in many human diseases. This article reviews briefly the regulation of signaling mechanisms.

Background

The three major ras genes each encode 21 kDa proteins are localised to the cytoplasmic side of the plasma membrane [1] and act as intracellular switches in many of the signal transduction pathways that control cell growth and differentiation. The Ras proteins are members of the GTPase superfamily which share the property of cycling between active (GTP-bound) and inactive (GDP-bound) states [2,3].

Genomic structure and organisation of the three major RAS genes

The three Ras proteins are divided into 4 domains. There is 85% homology identity at their amino acids sequence. The human N-RAS gene is located on chromosome 1 (1 p22-p32) H-RAS on Chromosome 11 (11p15.1-p15.2) and K-RAS on Chromosome 12 (12p-12.1- pter) (O'Brien, 1984). There are also two human-RAS pseudogenes, H-RAS2 (on the X chromosome) and K-RAS (on chromosome 6). The three major Ras genes have a common structure consisting of four coding exons (numbered1-4) and a 5' non-coding exon (o) [4]. The K-RAS gene has two alternative fourth exons (exons 4A and 4B) encoding two isomorphic proteins [5]. Because the intron structures of the three genes vary greatly in size, there are marked differences in the size of these genes. Thus, the coding sequence of human N-RAS spans more than 7 kbp, H-RAS spans about 3 kbp and K-RAS more than 35 kbp [6]. H-RAS and N-RAS proteins each consist of 89 amino acids whereas K-RAS contains 188 amino acids [5].

Until recently, there was no clear evidence for function differences between biological activity of N-, H-, and K–RAS although their coding sequences are highly conserved [3]. Nevertheless, in many human malignancies there is a bias in favor of mutation of one of the three Ras genes [7]; while this may reflect the known tissue–specific difference expression of the different Ras isoforms or the action of different mutagens in different malignancies, it is also consistent with there being distinct functions of the three Ras proteins. In support of this, recent work from our laboratory has clearly indicated that H-RAS is more transforming than both N- and K-RAS in fibroblasts, while, N-RAS is more transforming in haemopoietic cells.

RAS activation

In quiescent cells of p21 Ras exists primarily in the inactive (GDP-bound) from. Upon activation to the GTP-bound state, p21 RAS can interact with a variety of effector molecules that transmit downstream signals [8-10].

Activation of normal Ras proteins is best understood for ligands (e.g., growth hormones and cytokines) which bind to receptor tyrosine kinase (RTKs) the cell surface (Satoh et al.,) [11]. Binding of ligand to RTKs leads to dimerization of these receptors and autophosphorylation selective thyrosins residue in cytoplasmic domain of the receptor [12]. These frequently act as binding sites for signalling molecules (such as adaptor protein) which contain SH2 domains, e.g., the growth factor receptor–bound protein 2 (GRB2) [13]. The SH3 domains of adaptor molecules then bind to a guanine nucleotide exchange factor (GEF) of which the best described is Son of sevenless (Sos) protein. The GRB2/Sos complex appears to be very important in Ras activation [14]. Indeed the principal function of GRB2 is thought to be recruitment of SOS to interact with Ras-GDP [15]. This reaction leads to the release of the GDP and the Ras protein then binds GTP to form Ras-GTP (active), which can then activate downstream effectors.

Normally the active (GTP-bound) state of Ras is transient due to its intrinsic GTPase activity which hydrolyses Ras-GTP to the inactive (Ras-GDP) state. However, the intrinsic GTP-ase activity of Ras protein is weak and insufficient under physiological conditions to

maintain Ras in an inactive form. This regulatory activity of hydrolysis of Ras is strongly stimulated by a family of proteins known as GAP.

Signal transduction pathways involving Ras:

Raf-dependent pathway

The Raf proteins, which are serine/threonine kinases, are essential for Ras-induced proliferation and transformation [6,16]. Active Ras binds to Raf localizing it to the plasma membrane [17,18] where it can bind to and phosphorylate MEK mitogen activated protein kinase (MAPK) extracellular signal-related kinase (ERK)Kinase) [19,20]. MEK then phosphorylates and activates MAP kinase, another serine/threonine kinase, which ultimately activates transcription factors in the nucleus e.g. Fos, Jun and c-Myc [21,22] (Figure 1). This is a simplified scheme since Raf-MAP Kinase pathway is complex and many modifications have been described indifferent cell types (Figure 2).

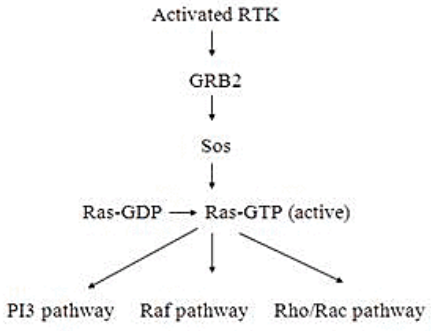

Figure 1: Signal transduction pathway involving Ras

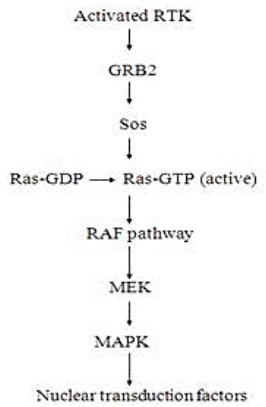

Figure 2: Raf dependent pathway

PI3K-dependent pathway

PI3K (phosphatidylmositol-3-OH kinase) has also been clearly demonstrated to be associated with Ras proteins and the ability of activated Ras to stimulate PI3K has been shown to be important in cellular transformation by Ras protein [23,24]. PI3K consists of 2 subunits: a catalytic (p110) and regulatory (p85) subunits (Carpenter and Cantley, 1990). Ras appears to act both upstream and downstream of PI3K. Evidence that Ras is upstream of PI3K came from the observation that Ras-GTP stably binds to the p110 sub-unit.

In conclusion, altered Ras pathway signaling may contribute to the development of several human cancers.

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