Review article

Signal Transduction Pathway in Chronic Leukemia

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Abstract:

It is becoming progressively clearer that the three RAS genes, N-. H-and K-RAS, encode 21 kDa proteins which act as intracellular switches, playing important roles in the signal transduction pathway that control cell development and maturation. These three genes are profoundly homologous, yet more recent findings indicate they have important roles in the functions various cell types playing focal roles in numerous human infections. This article briefly reviews the regulation of RAs-dependent signaling mechanisms.

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Background

The three major Ras genes each encode 21 kDa proteins that are restricted to the cytoplasmic aspect of the plasma membrane[1] acting as intracellular switches to a large extent in the signal transduction pathways that control cell development and differentiation. The Ras proteins are associated with the GTPase superfamily and share the property of cycling between dynamic (GTP-bound) and latent (GDP-bound) states[2].

Genomic Structure and Organisation of Three Major RAS Genes

The three Ras proteins are separated into 4 domains exhibiting 85% homology in arrangement of their amino acids. The human N-RAS gene is situated on chromosome1 (p22-p32 H-RAS on Chromosome 11 (11p15.1-p15.2) and K-RAS on Chromosome 12 (12p-12.1-pter). There are in addition two human-RAS pseudogenes, H-RAS2 (on the X chromosome) and K-RAS (on chromosome 6). The three noteworthy Ras genes have a typical structure comprising of four coding exons (numbered1-4) and a 5' non-coding exon (o)[3]. The K-RAS gene has two exons 4A and 4Bthat encode two isomorphic proteins[4]. Since the intron structures of the three genes change significantly in size, there are marked contrasts in the span of these genes. Along these lines, the coding succession of human N-RAS traverses more than 7 kbp, H-RAS ranges around 3 kbp and K-RAS more than 35 kbp[4]. Each H-RAS and N-RAS protein comprises of 89 amino acids, although K-RAS contains 188 amino acids[5].

Until relatively recently, there was no reasonable confirmation for contrasting capacity between the organic movement of N-, H-, and K–RAS in spite of the fact that their coding groupings are profoundly conserved. In numerous human malignancies, there is a predisposition for transformation of one of the three Ras genes[6]. While this may mirror the known tissue–specific articulation of the diverse Ras isoforms or the activity of various mutagens in various malignancies, it is likewise balanced with there being unmistakable elements of the three Ras proteins. In support of this notion, recent work from our group has clearly demonstrated that H-RAS exhibits greater changes compared with both N-and K-RAS in fibroblasts, while, N-RAS has greater variability in haemopoietic cells.

RAS Activation

In resting cells p21 Ras is present has an inert (GDP-bound) form. Upon activation to the GTP-bound state, p21 RAS can interface with an assortment of effector moieties that subsequently transmit downstream signals[7-8]. Initiation of typical Ras proteins is most common for ligands (e.g., development hormones and cytokines) which bind to receptor tyrosine kinase (RTKs) on the cell surface[9]. Dedicated ligands for RTKs promotes dimerization of these receptors and autophosphorylation in particular tyrosine accumulation in the cytoplasmic region of the receptor[10]. These often act as binding sites for signaling molecules, (for example, connector proteins) which contain SH2 regions, e.g., the development variable receptor–bound protein 2 (GRB2) [11]. The SH3 spaces of connector elements then bind to a guanine nucleotide exchange

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component (GEF) of which the best depicted is Son of sevenless (Sos) protein. The GRB2/Sos complex plays a key role in Rasactivation[12]. Indeed, the key roleof GRB2 is thought to be recruitment of SOS to cooperate with Ras-GDP[13]. This response prompts the recruitment of GDP and Ras proteins then bind GTP to giving Ras-GTP (dynamic), which can then activate down stream effectors. Usually, the dynamic (GTP-bound) condition of Ras is transient because of its natural GTPase movement which hydrolyses Ras-GTP to the latent (Ras-GDP) state However, the characteristic GTP-ase movement of Ras protein is transient and under physiological conditions may not maintain Ras in a latent structure. This controlling action of hydrolysis of Ras is clearly controlled animated by a group of proteins known as GAP.

Signal Transduction Pathways Involving Ras:

Raf-dependent pathway

The Raf proteins, which are serine/threonine kinases, are key for Ras-incited multiplication and differentiation [5,14]. Dynamic Ras binds to Raf confining it to the plasma membrane[15] where it can bind to and phosphorylate MEK mitogen actuated protein kinase (MAPK) and extracellular signal related kinase (ERK) Kinase)[16]. MEK then phosphorylates and activates MAP kinase, another serine/threonine kinase, which eventually activates translation components in the nucleus eg. Fos, Jun and c-Myc[17] (Figure 1). However, the Raf-MAP Kinase pathway can be unpredictable and numerous adjustments have been depicted in unrelated cell types (Figure 1).

PI3K-Dependent Pathway

PI3K (phosphatidylmositol-3-OH kinase) has in additionally been shown to be connected with Ras proteins and the capacity of initiated Ras to enhance PI3K activity appears to be critical in the cell functions initiated by Ras protein[18]. PI3K comprises of 2 subunits: a synergistic (p110) and organizing (p85) subunit. Ras appears to act both upstream and downstream of PI3K. Proof that Ras acts upstream of PI3K originated from the observation that Ras-GTP progressively binds to the p110 subunit. In conclusion, furthering our understanding of the

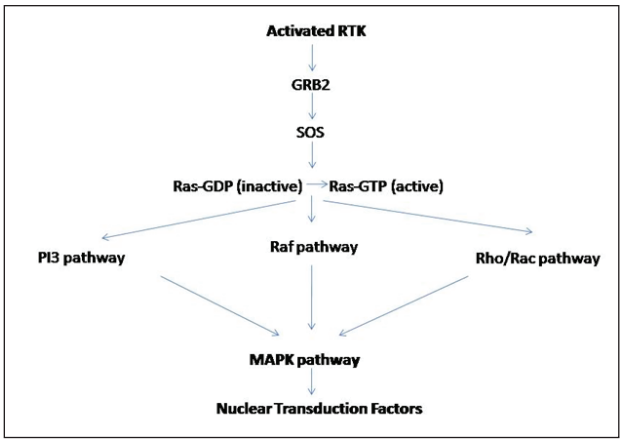

Figure 1: Signal transduction pathway involving Ras and Raf.

Ras pathway signaling may aid the development of improved therapies for a number of human diseases.

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