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Review

RAS signalling in energy metabolism and rare human diseases☆

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ABSTRACT

The RAS pathway is a highly conserved cascade of protein-protein interactions and phosphorylation that is at the heart of signalling networks that govern proliferation, differentiation and cell survival. Recent findings indicate that the RAS pathway plays a role in the regulation of energy metabolism via the control of mitochondrial form and function but little is known on the participation of this effect in RAS-related rare human genetic diseases. Germline mutations that hyperactivate the RAS pathway have been discovered and linked to human developmental disorders that are known as RASopathies. Individuals with RASopathies, which are estimated to affect approximately 1/1000 human birth, share many overlapping characteristics, including cardiac malformations, short stature, neurocognitive impairment, craniofacial dysmorphy, cutaneous, musculoskeletal, and ocular abnormalities, hypotonia and a predisposition to developing cancer. Since the identification of the first RASopathy, type 1 neurofibromatosis (NF1), which is caused by the inactivation of neurofibromin 1, several other syndromes have been associated with mutations in the core components of the RAS-MAPK pathway. These syndromes include Noonan syndrome (NS), Noonan syndrome with multiple lentigines (NSML), which was formerly called LEOPARD syndrome, Costello syndrome (CS), cardio-facio-cutaneous syndrome (CFC), Legius syndrome (LS) and capillary malformation–arteriovenous malformation syndrome (CM-AVM). Here, we review current knowledge about the bioenergetics of the RASopathies and discuss the molecular control of energy homeostasis and mitochondrial physiology by the RAS pathway.

1. RAS – MAPK pathway

The RAS/MAPK pathway transduces extracellular input in the form of growth factors and small molecules to the intracellular environment. This pathway has been studied extensively in the context of oncogenesis since its dysregulation is one of the primary causes of cancer. RAS gene somatic mutations are found in a variety of human tumour types and in approximately 20% of malignancies [1] (Fig. 1). In addition, germline mutations (Table 1) that activate RAS/MAPK signalling are responsible for the "RASopathies," a group of rare human developmental diseases that affect more than 400,000 individuals in the United States alone [2] (Table 2). Finally, abnormal RAS activity may also play a significant role in autism and other neurological disorders [3]. In this review article, we will discuss the impact of RAS activating germline mutations on the reprogramming of energy metabolism pathways, and the link with human rare genetic diseases (RASopathies).

RAS genes exist as a multigene family that includes *HRAS*, *NRAS*, and the two splice variants of *KRAS*: *KRAS4a* and *KRAS4b*. All four RAS isoforms contain identical residues in the first half of the GTPase domain (G-domain) and share 82% sequence identity in the second half of the G-domain. The end of the C-terminal domain exhibits significant sequence diversity among RAS isoforms and constitutes the "hypervariable region (HVR)." Moreover, KRAS4b is the only *RAS* gene that is not palmitoylated and contains a polybasic region [2]. The RAS family is activated through growth factors that bind to receptor tyrosine kinases (RTK), G-protein-coupled receptors, cytokine receptors and extracellular matrix receptors. The binding of a growth factor triggers RTK autophosphorylation and interaction with the adaptor protein GRB2 (growth factor receptor-bound protein 2). Then, GRB2 binds to SOS proteins, which are recruited to the plasma membrane (Fig. 2). RAS proteins are binary molecular switches that cycle between the active guanosine triphosphate (GTP)-bound and inactive guanosine diphosphate (GDP)-bound states. The conversion from the inactive GDP-bound form to the active GTP-bound form is stimulated by guanine nucleotide-exchange factors (GEFs), including SOS proteins, and the opposite reaction is mediated by GTPase-activating proteins (GAPs),

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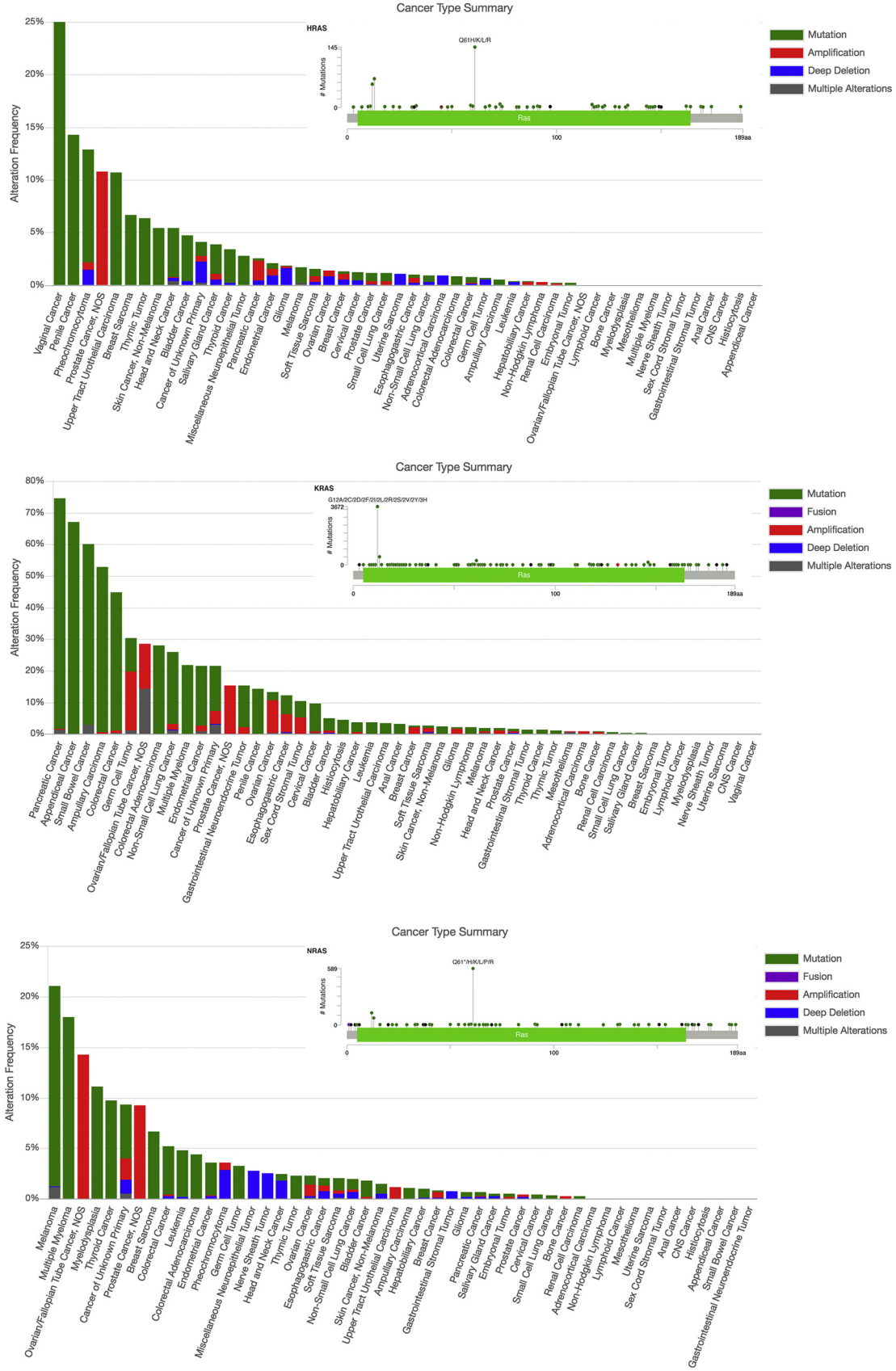

Fig. 1. *RAS* mutations in human tumours. Mutations in *HRAS* (A), *KRAS* (B) and *NRAS* (C) have been found in a variety of human tumours. Mutations include gene amplification, gene deletion or point mutation. The site of mutation on *HRAS*, *KRAS* or *NRAS* is shown in the "lolipop" representation. These data were obtained from the CBioportal (http://www.cbioportal.org/).