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Review

Herpesviruses: Hijacking the Ras signaling pathway

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ABSTRACT

Cancer is the final result of the accumulation of several genetic alterations occurring in a cell. Several herpesviruses and especially gamma-herpesviruses have played an important role in Cancer Biology, contributing significantly to our comprehension of cell signaling and growth control pathways which lead to malignancy. Unlike other infectious agents, herpesviruses persist in the host by establishing a latent infection, so that they can reactivate periodically. Interestingly, some herpesviruses are able to either deliver or induce the expression of cellular oncogenes. Such alterations can result in the derailment of the normal cell cycle and ultimately shift the balance between continuous proliferation and programmed cell death. Herpesvirus infection employs key molecules of cellular signaling cascades mostly to enhance viral replication. However, most of these molecules are also involved in essential cellular functions, such as proliferation, cellular differentiation and migration, as well as in DNA repair mechanisms. Ras proteins are key molecules that regulate a wide range of cellular functions, including differentiation, proliferation and cell survival. A broad field of medical research is currently focused on elucidating the role of *ras* oncogenes in human tumor initiation as well as tumor progression and metastasis. Upon activation, Ras proteins employ several downstream effector molecules such as phosphatidylinositol 3-kinase (PI3-K) and Raf and Ral guanine nucleotide-dissociation stimulators (RALGDS) to regulate a cascade of events ranging from cell proliferation and survival to apoptosis and cellular death. In this review, we give an overview of the impact that herpesvirus infection has on the host-cell Ras signaling pathway, providing an outline of their interactions with the key cascade molecules with which they associate. Several of these interactions of viral proteins with member of the Ras signaling pathway may be crucial in determining herpesviruses' oncogenic potential or their oncomodulatory behavior. The questions that emerge concern the potential role of these molecules as therapeutic targets both for viral infections and cancer. Understanding the means by which viruses may cause oncogenesis would therefore provide a deeper knowledge of the overall oncogenic process.

1. Introduction

1.1. Ras signaling pathway

Ras proteins are membrane-bound molecules that regulate a wide range of cellular functions, including differentiation, proliferation and cell survival [1]. A broad field of medical research is currently focused on elucidating the role of *ras* oncogenes in human tumor initiation as well as tumor progression and metastasis [2]. More specifically, Ras proteins are found to be mutated in many tumors such as melanoma, ovarian and lung carcinoma [3,4]. Genetic alterations of *ras* genes usually shift the balance between cell proliferation and cell death, towards continuing proliferation and differentiation. The role of *ras* genes during normal cellular function is dictated by the post-translational modification to which the proteins are subjected, which is mainly farnesylation. This process determines the final location of the proteins in the cell, primarily the plasma membrane, as well as their functionality. The enzyme farnesyl transferase links a farnesyl group (15-carbon isoprenoid) covalently to a cysteine residue located in the carboxy-terminal CAAX motif of Ras, allowing Ras to be

Abbreviations: BL, Burkitt's lymphoma; COX-2, cytochrome *c* oxidase subunit II; E, Early; EBNA, Epstein–Barr nuclear antigen; EBV, Epstein–Barr virus; EGF, Epidermal Growth Factor; EGFR, Epidermal Growth Factor Receptor; Elk, Ets-related transcription factor; ERK, extracellular regulated kinase; GDP, guanosine diphosphate; GTP, guanosine triphosphate; HCMV, Human Cytomegalovirus; HHV, Human Herpes Virus; HL, Hodgkin's lymphoma; HSV, Herpes Simplex Virus; IE, Immediate Early; IL, interleukin; JNK, c-Jun amino-terminal kinases; KSHV, Kaposi Sarcoma-associated Herpes Virus; L, Late; LAT, latency-associated transcript; LNA, latent nuclear antigen 1; MAPK, Mitogen-Activated Protein Kinases; MAPKK, MAPK kinase; MAPKKK, MAPK kinase kinase; MCD, multicentric variant of Castleman Disease; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; NGF, Neuronal Growth Factor; NPC, Nasopharyngeal Carcinoma; ORF, Open Reading Frame; PEL, Primary Effusion Lymphoma; PI3-K, phosphatidylinositol 3-kinase; PKR, RNA-activated protein kinase; RA, retinoic acid; RALGDS, Ral guanine nucleotide-dissociation stimulators; RTA, viral replication and transcriptional activation protein; TNF-α, tumor necrosis factor; TPA, 12-*O*-tetradecanoyl-phorbol-13-acetate; VZV, Varicella Zoster Virus

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anchored to the plasma membrane. It is known that the mis-positioned Ras proteins are non-functional, probably due to the inability of these proteins to employ their target enzymes and initiate signal transduction. Binding of ligands to tyrosine/kinase transmembrane receptors, autophosphorylates their tyrosine residues in the cytosol. The tyrosine residues serve as intracellular docking sites specific for several adaptor molecules such as members of the SOS family. Ras proteins remain inactive in the cell when they are bound to guanosine diphosphate (GDP), but become activated when bound to guanosine triphosphate (GTP) [5,6]. Ras is activated when ligand-bound receptors nucleate a complex including adapter molecules [e.g., Src homology and collagen (Shc; protein), Gab2, and growth factor receptor binding protein 2 (Grb2)], the phosphatase SHP-2, and guanine nucleotide exchange factors (e.g., SOS). Guanine nucleotide exchange factors bind to Ras and catalyze guanine nucleotide dissociation, which results in increased Ras-GTP levels. Ras activation is terminated by hydrolysis of GTP to GDP. This reaction is greatly accelerated by the GTPase-activating proteins p120GAP and neurofibromin.

Activation of Ras is responsible for the sequential phosphorylation of downstream molecules which amplify and transduce signals from the cell surface to the nucleus. More specifically, Ras proteins can employ up to 20 downstream effector molecules such as phosphatidylinositol 3-kinase (PI3-K) and Raf and Ral guanine nucleotide-dissociation stimulators (RALGDS) to regulate a cascade of events ranging from cell proliferation and survival to apoptosis and cellular death [7–12]. The activated Raf kinase, in particular, activates the MAPK cascade (Fig. 1). The MAPK cascade in the mammalian cell comprises three well-characterized protein kinases that are activated by protein phosphorylation: a MAPK kinase kinase (MAPKKK), a MAPK kinase (MAPKK) and finally a MAPK. The final protein kinases (MAPKs) are the extracellular regulated kinase (ERK1/2), p38 kinases, ERK5 and the c-Jun amino-terminal kinases (JNK12/3). The Ras/Raf/MEK/ERK pathway is generally induced by cell surface receptors such as the Epidermal Growth Factor Receptor (EGFR), whereas the p38 and JNK kinases respond to stress signals as well as growth factor expression [13].

1.2. Herpesviruses and the Ras pathway

The Ras pathway molecules respond to various extracellular stimuli which eventually determine the fate of the cell. Environmental, chemical and infectious agents have the ability to affect the signaling process in the cell, altering its physiological function. Human herpesviruses are of particular interest, since they are able to either induce tumor initiation (oncogenic viruses), or regulate tumor behavior (oncomodulatory viruses). Interestingly, 17.8% of worldwide cancer cases are attributed to infectious agents, while 12.1% of the total cancer cases are caused by viral infections [14]. Essentially, the above 12.1% represents almost 70% of the total (17.8%) caused by infectious agents.

Bearing these epidemiological data in mind, as well as the causative role of herpesviruses in several human diseases, involving key signaling molecules of the host, we review this family of viruses focusing on the Ras signaling pathway. Eight human herpesviruses have been extensively studied and several of them have been associated with the oncogenic Ras signaling pathway. In more detail,

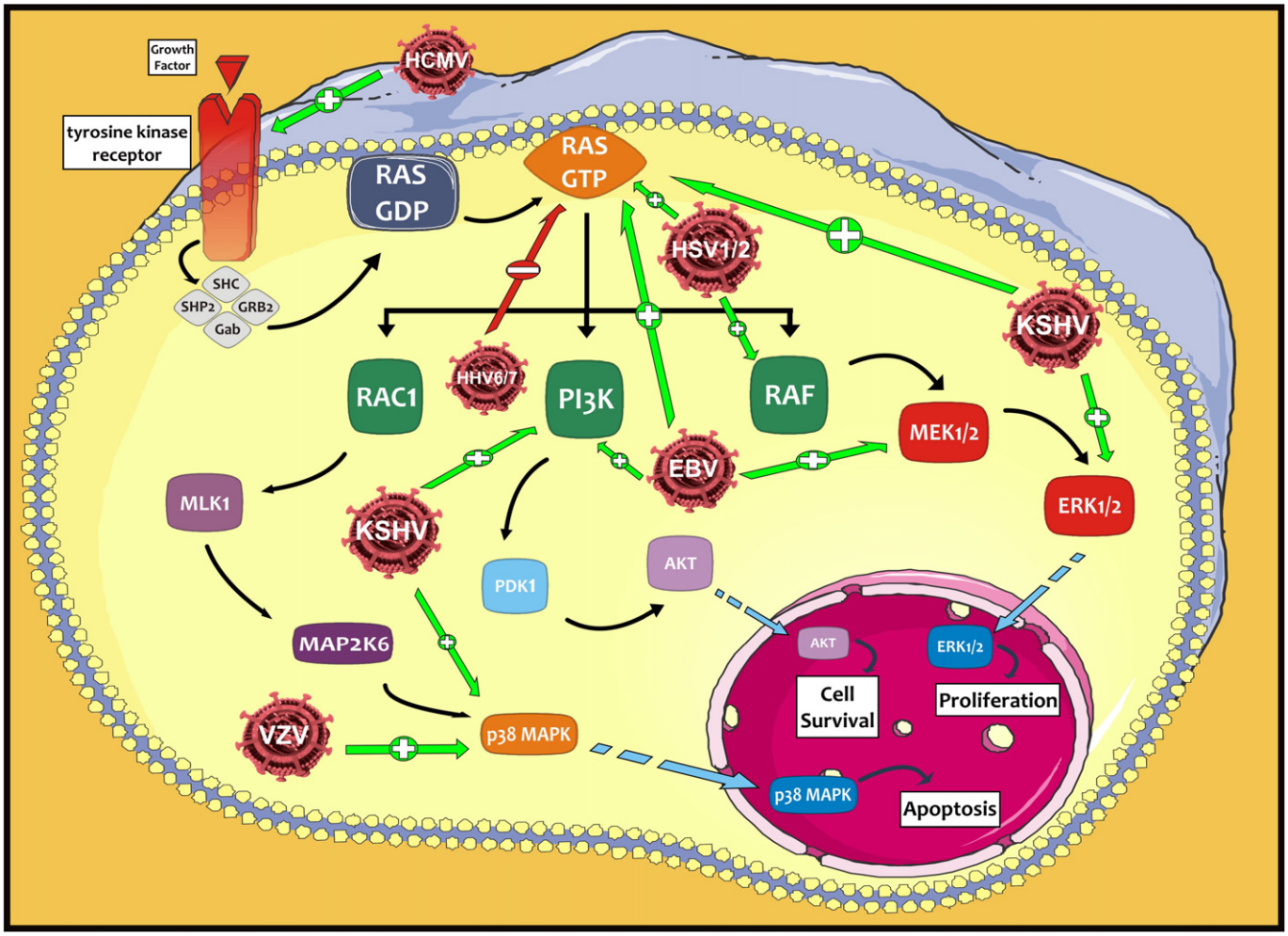

Fig. 1. Host cell Ras signaling pathway. The key mediators of the pathway are represented. Interactions between herpesviruses and host cell proteins are illustrated, indicating whether the virus up-, or down-regulates a specific cellular molecule.