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Review

The IGF axis in HPV associated cancers

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ABSTRACT

Human papillomaviruses (HPV) infect and replicate in stratified epithelium at cutaneous and mucosal surfaces. The proliferation and maintenance of keratinocytes, the cells which make up this epithelium, are controlled by a number of growth factor receptors such as the keratinocyte growth factor receptor (KGFR, also called fibroblast growth factor receptor 2b (FGFR2b)), the epithelial growth factor receptor (EGFR) and the insulin-like growth factor receptors 1 and 2 (IGF1R and IGF2R). In this review, we will delineate the mutation, gene transcription, translation and processing of the IGF axis within HPV associated cancers. The IGFs are key for developmental and postnatal growth of almost all tissues; we explore whether this crucial axis has been hijacked by HPV.

Contents

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1. Introduction

1.1. Viral replication in squamous tissue

HPVs infect epithelial surfaces, producing either benign or malignant lesions in genital and oral sites, depending on the papillomavirus type [1,2] and duration of infection. The most common low-risk viruses infecting mucosal surfaces are HPV types 6 and 11, and the most prevalent oncogenic viruses are the high-risk HPV types 16, 18, and 31. All of the papillomaviruses HPVs replicate in the stratified epithelium, with maximal replication of the viral DNA genome observed in the granular layer of the outer part. The cells in this region of the epithelium are terminally differentiated and undergoing a process of controlled cell death, as evidenced by the enucleated cells that form the cornified layer (the outermost layer of the epithelium). Because the virus relies on host cellular components for replication of its genome, it needs to stimulate cells back into the cell cycle and into S-phase, so that there is a plentiful supply of the DNA replicative machinery. As a consequence, the virus de-regulates the normal cell cycle. Which when the infection is caused by oncogenic HPV types, it may result in the initiation of premalignant lesions [3,4].

Replicating HPVs also have to maintain the integrity of the cell, probably through stimulation of signaling pathways that are involved in normal cell survival. Human keratinocytes need to survive for up to 2 weeks after they detach from the basement membrane and start to stratify [5]. They move from an integrin-mediated attachment and survival stimulus to a cell-to-cell contact survival stimulus, which is driven in part by E-cadherin interactions between cells. The HPV genomes will segregate with the cells as they leave the basement membrane, and viral proteins may enhance cell survival by modulating E-cadherin signaling, because cells infected with viruses are stressed and may die through an apoptotic pathway to limit viral replication. Many viruses code for proteins that have anti-apoptotic activity, so that cells survive long enough to allow successful viral replication [6]. Therefore, as well as stimulating terminally differentiating keratinocytes back into the cell cycle, the virus must ensure survival of the cells for successful virus propagation. The transforming capabilities of high risk HPVs are largely due to the functions of the protein products of the early genes E6 and E7 [7]. The combined functions of E6 and E7 impact greatly on the processes of cell division, through degradation of p53 and the retinoblastoma-family proteins (pRb, p107 and p130) and also result in impaired differentiation. This, if the HPV infection is not resolved, can ultimately lead to tumourigenesis. One signaling pathway essential for the transforming capability of high-risk HPVs E6 and E7 is the IGF axis.

2. The IGF axis

2.1. Overview

The core of the IGF axis is comprised of two ligands: Insulin-like growth factors I and II (IGF-I and IGF-II), two receptors: IGF1R and IGF2R, and six IGF binding proteins (IGFBP1-6). Initial studies seeking to identify systemic regulators of growth (the somatomedin hypothesis [8], it was proposed that growth hormone (GH) secreted from the pituitary caused the release of substances into the circulation, which indirectly mediated GH dependent growth. Somatomedins were later identified as IGF-I and IGF-II. With respect to the GH/IGF-I axis, it has been thought that circulating or locally produced IGF-I mediates [as a mediator (somatomedin) of GH (somatotropin)] the growth-promoting actions of GH [9–11]. The liver is the major source for circulating, or endocrine, pool of IGF-I. However, other tissues, including the brain, kidney, and muscle, can produce their own paracrine/autocrine source of IGF-I. The general consensus is that limiting liver IGF-I does not inhibit the growth of the tissues/cells as they make their own IGF-I and this local production is necessary and sufficient to support growth of the tissue in question. Key evidence implicating IGFs in the development of cancer are that mutations in GH, which ultimately reduce circulating IGF levels are associated with reduced susceptibility to cancer [12,13]. Combining this together with experimental evidence of the pro-proliferative, pro-migratory and pro-invasive functions of the ligands implies a strong correlation with tumourigenesis [14]. These issues of canonical actions of the IGF system in carcinogenesis from a clinical perspective are reviewed in detail in another paper of the SI ("Insulin-like growth factor (IGF) axis in cancerogenesis").

When exploring the role of the IGF/IGFR pathway in cancer there have been two major avenues of research: i) assessment of the availability of the ligand to bind to the receptor, and ii) assessment of receptor levels within the tumour. While we recognize that there are many more players that modulate bioavailability of the ligands and the signaling pathway triggered by receptor activation, the following sections review the family of ligands, binding proteins, and receptors that contribute to the ultimate activity of this pathway.

2.1.1. IGF-I and its many isoforms

IGF-I is highly regulated at the mRNA and protein level. Specifically, there are two classes of the IGF-I isoforms, namely class I and II precursors, and they are constituted by the interchangeable utilization of exons 1 and 2, respectively. These exons encode a portion of the signal peptide(s) and their use appears to be dependent on two different promoters [15]. The predominant IGF-I transcript excludes Exon 5, splicing Exon 4 directly to Exon 6, and is defined as *class A*. The inclusion of rodent Exon 5 or a portion of human Exon 5, causes a frame shift in the open reading frame of Exon 6 and gives rise to a premature stop codon. This splice form (*class B* in rodents and *class C* in humans) only occurs in up to 10% of the *igf1* transcripts [16–18]. A third form found uniquely in humans (*class B*) contains only Exon 5, which is a significantly longer sequence (515 nucleotides) than in other species [19]. The prepropeptide expressed by the *igf1* gene is >90% identical in mammals [18,20], with alternative splicing resulting in multiple isoforms that retain the identical sequence for mature IGF-I peptide, although divergent C-terminal peptides are produced, called the E-peptides [15–17,21]. Due to differential exon 5 usage in humans, the E-peptides are only 50% homologous at the amino acid level.

IGF-I prepropeptides also require multiple processing steps prior to producing a mature IGF-I peptide that is 70 amino acids long and identical for all isoforms. The peptide precursor (proIGF-I) contains the E-peptide in addition to the domains in the mature peptide. A pentabasic motif near the end of the D-domain and preceding the E peptide (Lys65-X-X-Lys68-x-x-Arg71-x-x-Arg74-x-x-Arg77) contains two putative cleavage sites, Arg71, and Arg77. This motif is included in all classes of IGF-I. Cleavage at Arg71 is mediated by serine proteases from the subtilisin-related proprotein convertase family (SPC) [22]. SPCs are expressed in many tissues, and are critical to the intracellular processing of proteins destined for secretion (reviewed in [23]). The final removal of Arg71 is possibly accomplished by a carboxypeptidase.

The working model for IGF-I conversion from pro-peptide to mature protein denotes this cleavage to occur intracellularly. However, several reports have detected the secretion of proIGF-IA and rodent proIGF-IB from fibroblasts and myoblasts [24,25], and additional studies have found evidence of Pro-IGF-IA in the circulation [26,27]. Of the 9 SPCs, 7 are secreted or shed, and are possible candidates for cleaving IGF-I outside of the cell, even