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Review

Modulation of radiation sensitivity and antitumor immunity by viral pathogenic factors: Implications for radio-immunotherapy

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ABSTRACT

Several DNA viruses including Human Papillomavirus (HPV), Epstein-Barr virus (EBV), and Human cytomegalovirus (HCMV) are mechanistically associated with the development of human cancers (HPV, EBV) and/or modulation of the immune system (HCMV). Moreover, a number of distinct mechanisms have been described regarding the modulation of tumor cell response to ionizing radiation and evasion from the host immune system by viral factors. There is further accumulating interest in the treatment with immune-modulatory therapies such as immune checkpoint inhibitors for malignancies with a viral etiology. Also, patients with HPV-positive tumors have a significantly improved prognosis that is attributable to increased intrinsic radiation sensitivity and may also arise from modulation of a cytotoxic T cell response in the tumor microenvironment (TME). In this review, we will highlight recent advances in the understanding of the biological basis of radiation response mediated by viral pathogenic factors and evasion from and modulation of the immune system by viruses.

1. Introduction

More than two million cases of cancer worldwide are considered to be associated with infectious agents each year [1]. Over the last decades studies on the role of these infectious agents, including a multitude of viruses, in carcinogenesis have provided increasing insights into the mechanisms of viral cancer induction/progression and evasion of the host immune system to ensure long lasting viral persistence [2]. Moreover, there is growing evidence on the association of viral pathogenic factors with a modulation of the cellular radiation responses, therapeutic efficacy and patients' clinical outcome following radiotherapy (RT) and chemoradiotherapy (CRT). In addition, malignancies with viral etiology are considered more immunogenic and especially in case of Human papillomavirus (HPV) more sensitive to anti-cancer treatment [3,4]. Further, these cancers are important targets for immunotherapeutic options including immune checkpoint-inhibition [5,6]. In this review, we aim to describe recent advances in the understanding of the impact of viral infection on the modulation of radiation sensitivity, anti-tumor immunity and clinical consequences with special emphasis on head and neck (HNSCC) and anal squamous cell carcinoma (ASCC).

2. Characterization of the viruses

2.1. Human Papilloma virus

HPV is associated with a variety of benign tumors in humans such as warts [7]. Pioneering work from Harald zur Hausen revealed that certain HPV-types are associated with the development of cervical cancer [8]. Subsequently, other tumor entities including ASCC and HNSCC have been shown to be related to HPV infection. On the basis of tissue tropism and malignant potential, > 200 HPV-types have been classified covering cutaneous and mucosal types and, within the latter group, low- or high-risk types with regards to their oncogenic potential [9].

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Within the high-risk group, HPV-types HPV16, 18 and 33 remain the causative agents in the majority of HPV-associated cancers with HPV16/18-DNA prevalence rates ranging from approximately 70% in cervical cancer and 90% both in anal cancer and in HPV-positive HNSCC [10,11].

HPVs are double-stranded DNA viruses with a genome of approximately 8.000 base pairs encoding eight “early” (E) and “late” (L) viral proteins. These include HPV oncoproteins E5, E6, and E7, the regulatory proteins (E1 and E2) and the structural viral capsid proteins L1 and L2 [12]. On the molecular level, HPV oncoproteins, which are overexpressed in HPV-induced cancers and their precursors, can interact with a large number of cellular proteins leading to the deregulation or activation of regulatory and signaling pathways [13]. Among others, HPV E6 inactivates the tumor suppressor proteins TP53 via the ubiquitin ligase E6AP resulting in the inhibition of apoptotic cell death, disturbed cell cycles kinetics resulting in non-restricted proliferation under conditions of replication stress and genomic instability [14]. Similarly, HPV E7 binds the retinoblastoma (Rb) protein and targets it for proteasomal degradation, which results in the release of the transcription factor E2F1, which in turn fosters the expression of a multitude of S-phase genes like cyclin-dependent-kinase inhibitor $p16^{INK4a}$. The latter is associated with a promotion of progression through the cell cycle [15]. Apart from the regulation of these most prominent tumor suppressor proteins, E6 and E7 bind to various additional cellular targets, including human telomerase (hTERT) and DNA repair enzymes, and disrupt centrosome synthesis [16,17].

2.2. Epstein-Barr virus

EBV (or human herpesvirus 4), a member of the human herpesviruses family, was the first oncogenic virus reported to infect humans and to be associated with a multitude of malignancies including Hodgkin's or Burkitt's lymphoma, gastric and nasopharyngeal carcinoma (NPC) [18,19]. EBV, one of the most prevalent viruses in the human population can establish a life-long infection and, by evolving an ability to escape clearance by the host immune system contribute to cancer development and persistence. The genome of the enveloped DNA double stranded virus covers 85 open reading frames, including genes coding for proteins involved in B-cell and endothelial cell entry (gp350, BMRF-2), lytic replication (BRLF-1, BNLF2, BCRF1) mediating latency programs (Epstein–Barr encoded nuclear antigen (EBNA-1 - EBNA-3) and latent membrane proteins (LMP-1, LMP-2). For malignant transformation EBNA-1 and LMP-1 are essential [20]. EBNA-1 comprises a trans-activator of latent viral and host genes and is involved in segregation and persistence of the viral genome, TP53 degradation and oncogenesis [21]. LMP-1 is a functional homologue to the cytokine tumor necrosis factor (TNF) and mediates signaling by nuclear factor kappaB (NF-κB), activatorprotein-1 (AP-1), Janus kinase/signal transducer and activator of transcription (JAK/STAT), and the p38 pathway to dysregulate via p27 the cell cycle resulting in a G2/M arrest [21,22]. Further, LMP-1 has an impact on human telomerase reverse transcriptase (hTERT) activity via the $p16^{INK4a}$/Rb/E2F1 signaling pathway [23]. Notably, EBV was the first virus reported to encode > 40 mature small non-coding micro RNA species (miRNAs) targeting the 3′-untranslated region (UTR) of viral and/or cellular genes to transcriptionally regulate a multitude of functions [24]. These include proliferation, differentiation and evasion of the host immune response [19].

2.3. Human cytomegalovirus

HCMV (or human herpes virus 5) is a member of the human herpesvirus family that can cause life-threatening diseases in immunosuppressed individuals. In line with other herpesviruses, the prevalence in the human population is high [25]. The exact impact of HCMV in the pathogenesis of human malignancies remains elusive. Accordingly, as compared to HPV and EBV, HCMV is not considered to be an oncogenic virus [26,27], however, an association between HCMV and glioblastoma, colorectal, breast and prostate cancer that may impact treatment response and interrelationship with the immune system has been reported [28–30]. The genome of the DNA virus encodes for 250 proteins with molecular weights ranging from 10 to 200 kDa and 12 viral miRNA [31] affecting proliferation, invasion, inhibition of apoptosis or autophagy, promotion of angiogenesis and immune suppression [32].

3. Viral infection and intrinsic cellular radiation sensitivity

3.1. Intrinsic radiation sensitivity mediated by HPV

Radiation responses are mainly determined by the intrinsic ability of the cell to sense DNA damage and subsequently to facilitate a DNA damage response (DDR) and mediate DNA repair. Environmental factors, such as the oxygenation status may further modulate damage induction and cellular responses and consequently affect radiation sensitivity [33]. Historically, radiation effects have been attributed to the “five Rs” of radiation biology covering repair, re-oxygenation, redistribution in the cell cycle, re-population and radiosensitivity [34]. Several groups have hypothesized that viral oncoproteins may affect these mechanisms and play a pivotal role in tumor and cellular radiation sensitivity. Indeed, for HPV-positive HNSCC recent research has revealed that the virus hijacks the cellular machinery for DNA repair, alters cell cycle distribution, induces proliferation and displays unique kinetics of hypoxia during radiation treatment [35]. In line with that, an enhanced radiation sensitivity has been repeatedly reported for HPV-positive HNSCC cell lines when compared to HPV-negative ones. The mechanisms described involve a decreased DNA double-strand break repair capacity, associated with an enhanced radiation induced G2/M cell cycle-arrest [36,37] upregulation of low levels of residual wild-type TP53 and of multiple genes involved in TP53 signaling, increased apoptosis and caspase activity [38]. Further, downregulation of AKT in HPV-positive HNSCC lines has been associated with a hampered clonogenic survival [39,40]. Beside an interrelationship with TP53 and Rb, HPV oncoproteins E6/E7 bind to X-ray repair cross-complementing protein 1 (XRCC1), a factor required for the repair of DNA single strand breaks [41]. In addition, E6 impairs the fidelity of non-homologous end-joining (NHEJ) [42].

Another recent hypothesis includes a direct effect of $p16^{INK4a}$ expression in HPV-positive HNSCC, as the protein was shown to suppress RAD51 foci formation and consequently DNA-repair by homologous recombination (HR) to increase the frequency of micronuclei [43]. Additionally, $p16^{INK4a}$ overexpression was also linked to a decreased expression of thyroid hormone receptor interactor 12 (TRIP12) and a subsequently enhanced expression of the DDR ubiquitin ligase RNF168 which repressed DNA damage repair in part by inhibition of the HR repair pathway [44]. Most recently Liu et al. reported loss of transforming growth factor β (TGF-β) responsiveness in HPV-positive HNSCC cells and specimen resulting in miRNA mediated suppression of breast cancer type 1 susceptibility protein (BRCA1) and forkhead box protein 03 (FOX03) which negatively impacts on HR and the activity of the DNA damage-sensing kinase ataxia telangiectasia mutated (ATM), respectively [45]. Following transfection of HPV-negative cells with a E6/E7 expression construct, Gubanova et al. reported on a suppressor with morphogenetic effect on genitalia-1 (SMG-1) promoter hypermethylation and decreased expression to contribute to an enhanced radiation response. SMG-1 is a member of the phosphoinositide 3-kinase–related kinases (PIKK) family and has been shown to be associated with the DDR network [46].

While in sum evidence of a reduced DNA repair capability and enhanced radiation sensitivity of HPV-positive cells are accumulating, it also needs to be critically noted that the mechanisms reported are diverse, have mostly not been recapitulated by other groups and are often

based on mechanistic experiments in a very limited number of cell lines. In addition, inconclusive and conflicting results have been shown, e.g. no impact on clonogenic survival in TP53wt colon carcinoma cells engineered to express E6 and E7 [47] or by knockdown of E6 and E7 in cervix carcinoma cells [48].

3.2. Intrinsic radiation sensitivity mediated by EBV and HCMV

Major research on the modulation of radiation response by EBV is focused on LMP-1, which is expressed in the majority of EBV-associated malignancies. LMP-1 represses the repair of DNA double strand breaks (DSBs) by the inhibition of phosphorylation and activity of DNA-dependent protein kinase (DNA-PKcs), a key enzyme of NHEJ pathway in nasopharyngeal carcinoma (NPC) [49] and by repression of ATM [50]. Further, LMP-1 reduces phosphorylation of AMP-activated protein kinase (AMPK) thus changing its subcellular location [49] and mediates glycolysis and resistance to apoptotic cell death induced by ionizing radiation [51]. By analyzing mechanisms associated with the radiation response following down-regulation of LMP-1, an increase in vascular endothelial growth factor (VEGF) expression and tumor microvascular permeability by elevated phosphorylation of JNKs/c-Jun pathway have been shown by Yang et al. [52]. The same group further indicated that ATM upregulation by LMP-1 knockdown is mediated by the NF-κB pathway by direct promoter binding, and vice versa inhibition of ATM increases radiation responsiveness in NPC [53]. Importantly, an increased radiation resistance of LMP-1 transfected NPCs is in line with upregulation of stemness related markers (CD44) and downregulation of phosphorylation of the DDR proteins, checkpoint kinase 1 (Chk1), Chk2, TP53 and TP53-targeted pro-apoptotic genes [54]. Finally, EBV encoded miR-155 and microRNA BamHI-A region rightward transcript (miR-BART7) were recently shown to regulate radiation sensitivity via suppressing the ubiquitin-like chaperon Ubiquilin-1 (UBQLN1) expression [55], and by targeting glutamine-fructose-6-phosphate transaminase (GFPT1). GFPT1 is a key enzyme of the hexosamine signaling pathway, controlling the immunomodulatory cytokine TGF-ß1 expression [56]. Finally, EBV encodes a variety of proteins such as BHRF1, EBNA-1, and miR-BARTs, that are implicated in resistance to apoptosis. For example, BHRF1 encodes a 17 kDa putative transmembrane protein with a sequence and functional homology to the anti-apoptotic Bcl-2 proto-oncogene that inhibits intrinsic activating pathways [57] [312].

Concerning the role of HCMV on radiation response, Rourke et al. reported on a modulation of DDR as assessed by a micronucleus assay in peripheral blood lymphocytes from patients with glioblastoma, indicating enhanced radiosensitivity in infected cells [58]. The underlying molecular mechanisms, however, remain elusive.

In summary, viral pathogenic factors impact on cellular radiation response on multiple levels with modulation of the DNA-damage repair machinery to be the most common point of attack. Mechanisms associated with the molecular and cellular radiation response in viral infected malignant cells are depicted in Fig. 1.

4. Viral infection and mechanisms of immune tolerance mediated by viral products

4.1. HPV infection and mechanisms of immune tolerance

There is growing consensus that mutational burden and viral etiology are associated with modulation of the tumor microenvironment (TME) affecting stromal architecture, tumor vasculature and immune cell infiltration/activation [59,60]. Primary tumors are commonly regarded to mount an immune suppressive TME to promote cancer progression and treatment resistance [61,62]. This is facilitated by a multitude of mechanisms for tumor immune escape [63], predominantly by suppressive immune cells such as tumor-associated macrophages (TAMs) [64], myeloid-derived suppressor cells (MDSCs) [65] and regulatory CD4, CD25 and transcription factor forkhead box P3 (FOXP3) positive regulatory T lympho- cytes (Tregs). Although the role of MDSCs in HPV-driven tumors is not fully elucidated, it is believed that reactive oxygen species (ROS) are involved in inhibition of T cell activation by downregulating the CD3zeta-chain of the T cell receptor complex [66].

Due to the accumulation of different mutations in the progression of tumor development and due to viral infection, transformed cells present a multitude of (neo)antigens that are regarded as foreign [67]. Accordingly, tumor control and rejection by the immune system requires the presentation of these target antigens, priming of an immune response in local lymph nodes, infiltration and differentiation of cytotoxic T cells (CTL) at the local tumor site(s) and finally activation of their effector functions. Processes of immune activation and tolerance have been studied in detail in HPV and other virus-associated tumors, revealing several strategies of immune evasion including intracellular and environmental mechanisms [68–70].

The intracellular strategies of viral immune evasion exerted by HPV cover low levels of viral E2-E7 gene expression [71] to hamper antigen detection by antigen presenting cells (APCs). HPV E5, E6, and E7 proteins were shown to selectively downregulate surface major histocompatibility complex (MHC) class I expression [72] and to hamper antigen processing and presentation [73]. Comparable mechanisms have been described for HCMV encoded genes that decrease MHC class I and II restricted antigen processing by retention of antigens within the endoplasmic reticulum [74,75]. EBNA-1 further harbors a cis-acting mechanism that facilitates suppression of its own mRNA translation and consequently antigen processing for MHCI-restricted presentation of EBNA-1 epitopes to cytotoxic T cells [76].

Moreover, HPV oncogene E7 perturbs DNA methylation and histone modification mechanisms by association with the DNA methyltransferase 1 (DNMT1) [77]. The latter is capable in silencing host cell CXCL14 chemokine [78] and adhesion molecules expression in line with a down regulation of Toll-like receptor 9 (TLR9) [79,80]. TLR9 preferentially binds exogenous viral or bacterial DNA, and triggers signaling cascades that result in pro-inflammatory cytokine and interferon (IFN) responses [81]. HPV has further evolved to evade the immune activation by binding to the transactivation domain of interferon response transcription factors (IRFs), resulting in a repression of peptide transporter associated with antigen processing 1 (TAP1), IFN-alpha/beta and monocyte chemotactic protein 1 (MCP1) expression [82,83].

A recent genome-wide gene expression analysis revealed that the HPV E2 protein down modulates expression of Interferon-kappa (IFN-κ), cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS) and the stimulator of interferon genes (STING) defense mechanism, while HPV E7 is reported to directly antagonize STING through its LXCXE motif [84,85]. cGas senses non-physiologic cytoplasmatic e.g. viral double stranded DNA, which in turn initiates innate immune signaling through downstream adapter proteins STING, IRF3 activation and type I IFN expression [86,87]. Radiation induces a type I IFN response by accumulation of cytosolic DNA and activation of the cGas/STING pathway, while ionizing radiation failed to stimulate type I IFN response in mice with a STING loss [88]. Also, STING expression is down-regulated in HPV-positive low-grade cervical squamous intraepithelial lesions compared with HPV-negative controls, indicating a putative clinical relevance of HPV oncogene mediated antagonization of the cGas/STING pathway [85].

In addition to intracellular evasion mechanisms, HPV affects cellular immune networks crucial to effective tumor clearance including T-helper (Th) cell and CTL responses. Similar to the macrophage subclassification, Th cells are grouped into Th1 and Th2 subtypes. Th1 cells mount a pro-inflammatory milieu with typical secretion of INF-γ, IL-2 and TNF-α, while Th2 cells are regarded as anti-inflammatory and secrete IL-4, IL-6, IL-10, [89]. In early HPV-associated lesions, Th2 cytokines such as IL-6 and IL-10 were prominent, while in high-grade epithelial lesions elevated levels of both Th1 (TNF-α) and Th2 (IL-10)

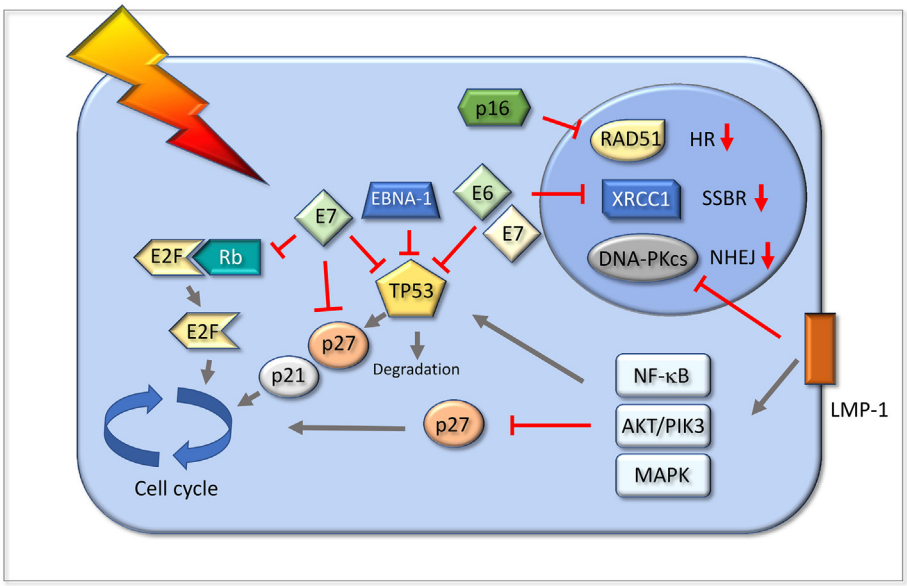

Fig. 1. Simplified model of the modulation of the cellular radiation sensitivity by viral components. HPV E6/E7 oncogenes impact on TP53 and retinoblastoma expression/activity and inhibit proteins of the DNA-damage response. EBV EBNA-1 is involved in TP53 degradation while LMP1 is involved in attenuation of DNA-PKcs activity and dysregulates the cell cycle by NF-κB, AKT/PIk3 and MAPK pathways. DNA-PKcs = DNA-dependent protein kinase catalytic subunit, EBNA-1 = Epstein–Barr encoded nuclear antigen 1, HR = homologous recombination, LMP-1 = Latent membrane proteins 1, MAPK = Mitogen-activated protein kinase; PIK3 = phosphatidyl-inositide3-kinases, Rb = Retinoblastoma, NHEJ = Non-homologous end joining, NF-κB = Nuclear factor kappa B, SSBR = Single strand break repair, XRCC1 = X-ray repair cross-complementing protein.

associated cytokines were upregulated reflecting a non-coordinated immune response [90].

Further, immunologically relevant mechanisms that induce T cell anergy and apoptosis cover the activity of immune checkpoint receptors, most prominent cytotoxic T lymphocyte antigen 4 (CTLA-4, CD152), programmed death (PD)-1 (CD279) and its ligand programmed death ligand-1 (PD-L1, CD274). While cancer and myeloid cells express PD-L1 by oncogenic activation such as the phosphoinositide 3-kinase (PI3K)-AKT or STAT pathways (innate resistance), PD-L1 expression on lymphocytes appears to be predominantly mediated by inflammation and genotoxic stress via IFN-γ secretion within the TME (adaptive resistance) [91,92]. Against this background, HPV can induce the expression of CTLA-4 and PD-1 on activated T and B cells, and enhance surface expression of PD-L1 on tumor and antigen-presenting cells [93].

4.2. EBV infection and mechanisms of immune tolerance

EBV binds to the neutrophilic surface by its envelope glycoprotein gp350, stimulates the expression of inflammatory cytokines IL-1α/IL-β, chemokines IL-8 and macrophage inflammatory protein (MIP)-1 [95,96] and launches apoptosis by modulating the first apoptosis signal receptor (Fas)/Fas ligand system [97]. EBV viral infection also impairs the phagocytic activity of primary monocytes by inhibiting protein kinase C (PKC) activity [98], and by hampering prostaglandin E2 and TNF-α production [99]. Moreover, LMP-1 induces Tregs to secrete IL-10, which in turn suppresses the proliferation of T-effector lymphocytes and the release of IFN-γ [100]. As reported before, EBV further encodes a multitude of viral miRNAs to dysregulate the expression of a variety of host miRNAs, which modulate the expression of immune-related molecules and signaling pathways. EBV miRNAs target the MHC peptide transporter TAP subunit and reduce the levels of TAP and MHC class I molecules expression, while down-modulation of the cytokine IL-12 decreases recognition by EBV-specific CD8-positive T cells [101]. The transport via exosomes of EBV regulated miRNAs and viral proteins further contributes to an immunosuppressive TME [102].

4.3. HCMV infection and mechanisms of immune tolerance

HCMV encodes numerous proteins and at least five miRNAs that impact on immune responses [69]. Genes encoded by the virus (IA, UL123-encoded IE2) directly impair type I IFN pathways [103], while viral mitochondria-localized inhibitor of apoptosis (vMIA), viral inhibitor of BAK oligomerization (vIBO) and viral inhibitor of caspase 8 (vICA) interfere with both intrinsic and extrinsic apoptosis pathways [104]. In addition, HCMV miR-UL112.1 targets the natural killer cell activating major histocompatibility complex class-I related chain B (MICB), thereby reducing natural killer cell activity. Along this line, miR-UL148D targets the chemokine (C-C Motif) ligand 5 (CCL5), miR-US25-2-3p inhibits inhibitors of tissue inhibitors of metalloprotease 3 (TIMP3) and miRUl112-3p targets the TLR2 and inhibits NF-κB signaling (reviewed in [105]). Finally, molecular mimicry exerted by HCMV comprises a strategy to subvert anti-viral immunity and to hijack a range of host encoded immunomodulatory markers. Unique mechanisms exerted by the virus cover the expression of proteins (e.g. UL21.5, US 27, US28, UL33, UL78, UL144) that act as receptors for host inflammatory chemokines and cytokines, reducing local chemokine/cytokine effectiveness [106]. Further, HCMV encodes a number of viral homologs of cytokines IL-8 (UL146) and immune- suppressive IL-10 (cmvIL-10:UL111a), mimicking human IL-10 activity in repressing pro-inflammatory TNF-α, IL-6 and IL-1 production to decrease MHC class II expression [107].

5. Prognosis and response to RT/RCT in virus associated tumors: Clinical findings

5.1. Response to RT/CRT in HPV associated tumors

HPV-associated malignancies of the head and neck, most pronounced in the oropharynx region, represent distinct clinicopathological features with unique biological properties that directly impact on clinical behavior [108,109]. Seminal findings by Fakhry et al. indicated that such tumors have improved prognosis and favorable survival rates with increased responsiveness to RT and CRT [3]. These observations were confirmed in a multitude of subsequent clinical studies [4,110–112]. Moreover, a detailed understanding of the genetic fingerprint and risk factors of HPV-associated tumors has led to attempts to personalize therapy, for example by a RT dose de-escalation. Chen and colleagues performed a single-arm, phase II study on reducing radiation dose from standard 70 to 60 or even 54 Gy in carcinoma of the oropharynx, resulting in similar progression-free survival time and an improved toxicity profile compared to historical regimens [113]. The improved clinical outcome observed in patients with HPV-positive HNSCC is attributed to multifactorial explanations covering reduced fields of cancerization, increased intrinsic radiation responsiveness and improved immune responses to viral infected tumor cells [114]. Patients with HPV-positive HNSCC for example mainly present

at a younger age at time of diagnosis as compared to HPV-negative ones [4,115,116] and with tumors that are less likely to be associated with tobacco or alcohol abuse.

5.2. HPV DNA detection and $p16^{INK4a}$ expression to predict response to RT/RCT

Concerning the outcome of patients with ASCC after standard CRT, Williams et al. used in-situ-hybridization to assess HPV-DNA status in a small cohort of 35 patients, but failed to detect a prognostic impact [117]. More recent studies using polymerase chain reaction (PCR), however, revealed a prognostic relevance of HPV16 DNA detection for multiple clinical endpoints including overall survival (OS), progression-free survival (PFS), disease-free survival (DFS) and loco-regional control (LRC) in ASCC and HNSCC [111,118–120]. A positive relationship between HPV status and CRT was further reported for HPV-positive vulva and penile cancer patients (as assayed by in situ hybridization, HPV genotyping and p16 immunohistochemistry) treated with CRT that displayed an improved LRC (penile cancer) or OS and PFS (vulva cancer) compared to HPV-negative ones [121,122]. We recently analyzed HPV16 DNA load defined as HPV16 DNA copies per beta-globin gene copy in a cohort of 95 patients treated by CRT for ASCC. A quantitative viral DNA load above the median predicted increased LRC and OS rates [123]. These findings were validated by other studies confirming better OS, DFS and PFS in HPV-16 DNA positive tumors [118,120,124]. More recently, an impact of quantitative HPV16/18 estimation and persisting HPV infection after radical RCT on LRC and recurrence-free survival (RFS) was further confirmed in locally advanced cervical cancer [125].

With regard to HPV surrogate immunohistochemical marker $p16^{INK4a}$ expression, there are conflicting reports on its impact on the clinical outcome after CRT for ASCC. Early studies indicated no significant prognostic influence for $p16^{INK4a}$ detection [126,127], or even higher incidence of local and distant recurrence in patients with high $p16^{INK4a}$ scores [128]. Three other reports indicated that patients with $p16^{INK4a}$ positive tumors have a significantly better PFS and LC but not OS [118,119,123], while two studies reported on better OS for $p16^{INK4a}$ positivity [120,124]. Notably, combining HPV-DNA with $p16^{INK4a}$ status may be useful to stratify ASCC patients into different prognostic subgroups as double positive (HPV-DNA+/p16+) patients displayed a significantly superior OS, LC and cancer specific survival [120,123,129,130].

5.3. HPV antibody levels as screening and prognostic markers

Mammals have evolved adaptive immune mechanisms to control viral infection with a humoral response to HPV-associated (neo)antigens to elicit host protective mechanisms [131]. Patients with HPV16 oncogene E6 seropositivity displayed a 200-fold increased risk to develop oropharyngeal cancer (OPC), a 75-fold increased risk for anogenital cancer and with a lower incidence carcinoma of the vagina, cervix, and penis. Moreover, these antibodies were detectable up to 10 years before tumor diagnosis, while being rare among cancer-free controls [132,133]. Accordingly, these findings argue for the development of highly specific biomarkers for HPV-driven malignancies that may be useful for screening/diagnostic approaches. Indeed, Holzinger et al. recently indicated HPV16 E6 seropositivity in 214 patients to be the best predictor of HPV16-driven OPC with a diagnostic accuracy of 97% [134]. Further, Hanna and colleagues investigated serum and salivary HPV16 E2, E6 and E7 antibody levels before and after definitive CRT in 44 patients with locoregionally-advanced OPC. When analyzed serially, median salivary E7 antibody levels decreased significantly post-CRT treatment indicating HPV clearance [135]. Moreover, high titers of E6 antibodies at diagnosis were associated with a significantly increased recurrence [136]. Another study, however, revealed that posttreatment HPV16 E6 antibody levels did not decrease significantly from the baseline and were not associated with the risk of recurrence. By contrast, pretreatment HPV16 E6 seropositivity was associated with an 86% reduced risk of local/regional recurrence in OPC [137]. Finally, by applying a custom programmable enzyme-linked immunosorbent (ELISA) assay in patients with HPV-related OPC, Dahlstrom et al. identified three HPV16-specific antibodies targeting E1, N-terminal E2, and E6, that were associated with improved OS and PFS [138].

5.4. Circulating HPV tumor DNA for prediction and to monitor disease progression

In HPV-related cancers, viral genomes are either present in episomal form or frequently integrated into the tumor cell DNA with the latter to be detectable in peripheral blood. [139]. Against this background, assessment of cell-free circulating HPV tumor DNA (ctDNA) may be useful not only to asses HPV status but also to monitor disease progression and recurrence in a tumor specific and non-invasive manner. In a recent investigation pretreatment HPV ctDNA was detected by a highly sensitive droplet digital PCR (ddPCR) in 29 of 33 patients with stage II–III ASCC. Although pretreatment detection failed to display a prognostic impact, HPV ctDNA became undetectable in most patients following CRT but three out of 18 patients (17%) displayed residual ctDNA levels: all these patients experienced rapid metastatic relapse after CRT [140]. Additionally, by using the ddPCR technique as mentioned before, an early and significant decrease of HPV ctDNA detection in the course of immune checkpoint anti-PD-1 therapy in a patient with metastatic ASSC [141] was reported. This observation provides a proof-of-concept that HPV ctDNA may be used as an early biomarker to monitor the efficacy of treatment. Lee et al. assayed HPV ctDNA by an amplicon-based next generation sequencing assay (HPV16-Detect) in locally advanced HNSCC treated with curative CRT. They demonstrated that HPV16 analysis in posttreatment samples in both a test and validation cohort correlates with residual disease (confirmed by PET-CT) at the primary site and in cervical lymph nodes, suggesting the potential of the assay in avoiding unnecessary surgical neck dissection procedures [142].

5.5. Response to RT/CRT in EBV associated tumors

In locally advanced NPC Song et al. showed that plasma EBV-DNA copy number levels (≥ 100 copies/ml) pre- and post-induction chemotherapy were independent predictive markers for LC and survival in response to RT [143]. In line with that, by performing a meta-analysis including 23 eligible studies, Zhang et al. recently described that EBV-DNA levels were significantly correlated with the outcomes of patients with NPC [144]. Notably, these data revealed superior OS, DFS, distant metastasis-free survival (DMFS) and locoregional relapse-free survival (LRRFS) in patients with negative or low level plasma EBV-DNA detection [145,146] and vice versa high viral load to predict poor prognosis in NPC treated with concurrent CRT. Apart from the detection of circulating EBV DNA, serum EBV viral capsid antigen (VCA) IgA antibodies showed a prognostic value in patients with undetectable pretreatment EBV DNA with an inferior 5-year PFS, DMFS and LRRFS associated with increased serum titers [147]. These results appear surprising when compared to the findings of a positive/high viral load being a positive prognostic factor in HPV-related malignancies, however, two major differences between the HPV- and EBV-studies have to be highlighted: first, viral load/positivity in HPV-related malignancies was always assessed in the pathological tumor specimens, whereas in patients treated for EBV-related NPC the evaluation was based on serum evaluation. This difference may explain the divergent prognostic values of these parameters, as other immune-related factors such as the leukocyte count display different prognostic values when assayed in the tumor or in the peripheral blood [148]. Further, the prognosis of NPC is dependent on distant control to a much higher degree compared with

ASSC. In a meta-analysis Blanchard et al. indicated that 22% of the patients with NPC initially treated with curative intent have later experienced distant metastases [149]. High levels of serum viral load could represent an early systemic dissemination of the disease with features as abundant circulating tumor cells.

Resistance to apoptosis is a hallmark of cancer cells and is associated with cellular radiation resistance [59]. Against this background EBV LMP-1 and EBNA-1 are reported to increase the expression of the inhibitor of apoptosis protein Survivin by the NF-κB and PI3K/Akt signaling pathway in T- and B cell lymphoma and to inhibit apoptosis [150,151]. As Survivin is further shown to impact on the cellular radiation response [152], this may comprise an additional mechanism contributing to a hampered treatment response.

Finally, viral oncogene LMP-1 expression is reported to be positively associated with metastatic disease in patients with NPC, indicating that the protein might be a feasible indicator to predict tumor dissemination [153].

5.6. Response to RT/CRT in HCMV carrying tumors

As compared to a growing body of evidence in relation to HPV and EBV infection, there is less data available on the prognostic impact of HCMV infection. In a case control study in patients with glioblastoma, Rahbar et al. indicated low levels of HCMV infection, as assayed by the number of virus positive cells is associated with long term (> 10 months) survival [154]. In addition, a lower level (< 25% cells) of infected cells in primary tissue specimens was associated with an extended time to tumor progression and an increased median survival after surgical resection [155]. Notably, a clinically significant opportunistic HCMV (re)activation during or after RT/chemotherapy of patients with high grade glioma was recently reported by Goerig and colleagues [156]. Accordingly, one may hypothesize that RT of tumors that contain HCMV particles results in local encephalitis/encephalopathy- and systemic viremia. In line with that, treatment of glioblastoma patients with an HCMV pp65 protein targeted vaccine resulted in a long-term improved PFS and OS [157].

6. Prediction of response to RT/CRT in virus associated tumors: the role of immune-markers

6.1. Immune markers in HPV associated malignancies

Paradoxically, despite its direct mechanistic involvement in tumorigenesis, HPV infection is associated with an increased immune response that may have a positive impact on treatment response and survival in patients treated with RT or CRT. In that context, it has been shown that HPV-associated tumors present viral antigens that elicit T-cell responses that participate in tumor rejection and long-term immune surveillance [158]. The importance of CD8-positive tumor infiltrating lymphocytes (TILs) in mediating response to RT/CRT and their prognostic impact in human malignancies is well established [61,159]. Along this line, several groups reported a strong infiltration of CD8-positive TILs and gene expression profiles, consistent with elevated T cell activation in HPV-positive HNSCC patients, to correlate with superior response to CRT and outcome [160,161]. Indeed, Welters et al. recently reported, that HPV-specific CD4+ and CD8+ T cells were detected in 64% of the TILs derived from HPV16-positive oropharyngeal carcinoma and were strongly associated with an increased OS, diminished numbers of lymph node metastases and smaller tumor sizes [158].

Patients with HNSCC showing high levels of CD8-positive cell tumor-infiltration exhibited improved OS, PFS and DMFS after definitive and postoperative RT/CRT [162]. In contrast, intratumoral abundance of CD4-positive T cells or FOXP3-positive Tregs were not of prognostic value in these settings [163,164]. The latter is consistent with a meta-analysis that failed to detect a significant prognostic value for CD4 or FOXP3 expression with regard to disease progression and patient survival in a multitude of tumor entities [165].

In a pilot study of 20 patients with locally advanced HPV associated diseases, CRT was shown to alter the immune landscape, with an increase in the numbers of MDSC, Tregs and T cells expressing PD-1 [166]. An altered landscape was recently confirmed by using bioinformatic tools and data from the Cancer Genome Atlas (TCGA), indicating that genes upregulated in HPV-positive HNSCC are enriched in immune-associated processes [167]. As such, the TME of HPV-positive HNSCC exhibited increased numbers of infiltrating B and T cells and lower counts of neutrophils as compared to their HPV-negative counterparts. Moreover, the ratio of tumoricidal (M1) to tumorigenic (M2) macrophages is higher in HPV-positive HNSCC [167]. Expression of PD-L1 is high in HNSCC tumors, with positivity being quoted between 18 and 85% across different investigations [168]. T cells from HPV-positive tumors express higher levels of PD-1, which may hamper proliferation and effector functions, but also correlates with improved prognosis [169]. We recently reported that HPV16 positivity strongly correlated with CD8 and PD-1 positive TILs, and tumor cell PD-L1 expression in patients with HNSCC treated with adjuvant CRT, especially in combination with high CD8 infiltration [170]. In conjunction with CD8, PD-L1 may thus represent a valuable prognostic marker that may guide treatment with checkpoint inhibitors in the context of HPV status. Relevant to the latter, recent clinical trials in patients with recurrent or metastatic HNSCC demonstrated first promising results using the PD-1 inhibitors nivolumab and pembrolizumab in terms of a significantly prolonged OS [171,172].

A proportion of patients with ASCC present with immunogenic tumors that are closely linked to HPV infection and viral load [173]. As for HNSCC, HPV-positive ASCC exhibited increased infiltration by immune cell populations, most pronounced CD8 positive T cells that correlated with a superior response to CRT and a lower incidence of local failure and improved DFS and OS [174–176]. Two recent studies showed that higher expression of PD-L1 correlated with worse outcome in ASCC [177,178], while another reported an elevated PD-L1 expression to be associated with superior local control and survival [175].

6.2. Immune marker in EBV associated malignancies

Ooft and colleagues reported on increased CD3-, CD4- and CD8-positive TIL infiltration in EBV-positive NPC, demonstrating a significant positive prognostic impact of elevated CD8 and PD-L1 detection and co-expression on DFS and OS [179]. The same group further reported on high FOXP3 count to be associated with increased OS in the entire group while no differences in M2 polarized TAMs was to be observed [180].

7. Therapeutic implications on radio-immunotherapy in virus-associated tumors

Current advances in cancer therapy arise from the therapeutic effects of immune checkpoint blockade (ICB) using antibodies for CTLA-4 and the PD-1/PD-L1 axis. These options have markedly improved management of several malignancies including melanoma, lung, renal, urothelial and intestinal carcinoma [91]. In addition to interests in testing these inhibitors, there also exists a strong basis to combine ICB with ionizing radiation that has been shown to induce “immunogenic” forms of tumor cell death [181,182]. Preclinical and clinical evidence indicates that RT can further elicit profound immune stimulatory effects. These include activation of the cGAS/STING pathway [88], secretion of inflammatory cytokines and danger signals (ATP, Calreticulin, High-Mobility-Group-Protein B1), upregulation of MHC molecules and antigen presentation, induction of the CD95 (Fas) receptor, upregulation of PD-L1, activation of pro-phagocytic signals and increased T-cell trafficking [183,184].

Accordingly, there are several lines of evidence supporting the

combination of ICB with RT especially in virus-associated tumors. Infection with HPV and EBV is associated with a higher immunogenicity as reported before and appears to highly correlate with a high CD8 and PD-1 TILs infiltration at baseline [173]. Against this background, data from the KEYNOTE-012 trial [172] on patients with PD-1 positive recurrent or metastatic HNSCC treated with the PD-1 inhibitor pembrolizumab reported on an increased proportion of overall response in patients with HPV-positive tumors (25%) as compared to negative ones (14%). An ongoing randomized phase II trial further investigates the addition of the PD-1 inhibitor nivolumab after CRT in locally advanced ASCC (NCT03233711). In this feasibility study, 9 patients (24%) out of 37 achieved a tumor response, which was complete in 2 patients. Notably, in the metastatic/recurrent setting, immunotherapy trials currently further test the efficacy of application of HPV-16/18 E6/E7 specific T-cells (NCT02379520), and a combination of T-cell receptor gene therapy targeting HPV-16 E7 with PD1-inhibition (NCT02858310).

The question on the most effective combination of RT and ICB in virus associated cancers, however, remains a matter of debate. Stratification based on molecular tumor characteristics including mutational load [185] and virus status in combination with TILs infiltration and tumor PD-L1 expression appears to be a reasonable approach as recent investigations have recommended studying these markers to characterize the tumor immune phenotype. Based on these parameters a four-group classification has been proposed that covers type I (TILs high/PD-L1 high) reflecting adaptive immune resistance, type II (TILs low/PD-L1 low) indicating immunologic ignorance, type III (TILs low/PD-L1 high) mediating intrinsic induction, and finally type IV (TILs high/PD-L1 low) mediating tolerance [186,187]. A recent report based on the cancer genome atlas (TCGA) including 32 tumor entities and n = 59,677 cases indicated a strong correlation between type I tumors and HPV-positivity [188]. These data were further supported by our own findings that patients with type I HNSCC and ASCC were significantly more common in HPV-positive immunogenic tumors [170,175]. This extended classification, covering virus status/viral load, CD8 TILs infiltration and PD-L1 expression for patient stratification at least in HPV associated malignancies is depicted in Fig. 2. In this model, patients with HPV high/TILs high/PD-L1 high are regarded to have a favorable prognosis after CRT and additive/synergistic effects of ICB may further improve the clinical outcome or may allow deintensified CRT regimes. In HPV high/TILs low/PD-L1 low, the use of CRT to stimulate infiltration of cytotoxic CD8-positive TILs displays a reasonable clinical approach that may be potentiated by adjuvant immunotherapy (treatment escalation). In patients with HPV-negative/TILs low PD-L1 high tumors showing a moderate prognosis, an (at least) additive effect between ICB and RT/CRT may be expected, dependent on other immunogenic factors, such as mutation-associated neoantigenes. Finally, in immunogenically “cold” HPV negative/TILs low/PD-L1 low tumors, ICB is considered less effective and RT/CRT might need to be combined with alternative therapeutic options. These may include molecularly targeted therapies using antibodies or small molecule inhibitors or immunotherapies others than checkpoint inhibition. A multitude of approaches have been developed to intensify efficacy of combined CRT and immunotherapy that may impact on future strategies for all types as mentioned before. For example, in a relapsed HPV-associated oropharyngeal, cervical, anal, vulvar and penile setting current trials test the application of HPV-16/18 E6/E7 specific T-cells generated from patient's blood and trained to kill HPV-infected tumor cells (NCT02379520). A further approach is combining the drug cisplatin with a synthetic p16 peptide fragment covering amino acids 37–63 in HPV-associated anogenital, and head and neck malignancies to analyze the ability to elicit a peptide specific T cell response (NCT02526316). Alternative approaches further cover immune stimulation by a live-attenuated Listeria monocytogenes vaccine ADXS11–001 targeting HPV-positive cells carrying the E7 oncoprotein which was tested in combination with standard CRT in patients with ASCC (NCT01671488). First published data indicate that ADXS11–001 can be safely administered and 8 of 9 assessable patients display progression-free diseases at a median follow-up of 42 months [189]. Finally, future strategies may further include the use of oncolytic viruses that selectively replicate and kill target tumor cells or can be genetically engineered in a tumor specific manner [190] broadening neoantigene-directed T-cell responses [191]. This is clinically evaluated within the KEYNOTE-137 trial, a phase Ib randomized study exploring the combination of Talimogene Laherparepvec (T-VEC GM-CSF) with the PD-1 inhibitor pembrolizumab in recurrent metastatic HNSCC (NCT02626000). T-VEC (also named OncoVEX), a live attenuated herpes simplex virus type 1 was engineered to selectively replicate in tumor cells and to express granulocyte macrophage colony-stimulating factor (GM-CSF) thus stimulating a systemic antitumor immunity.

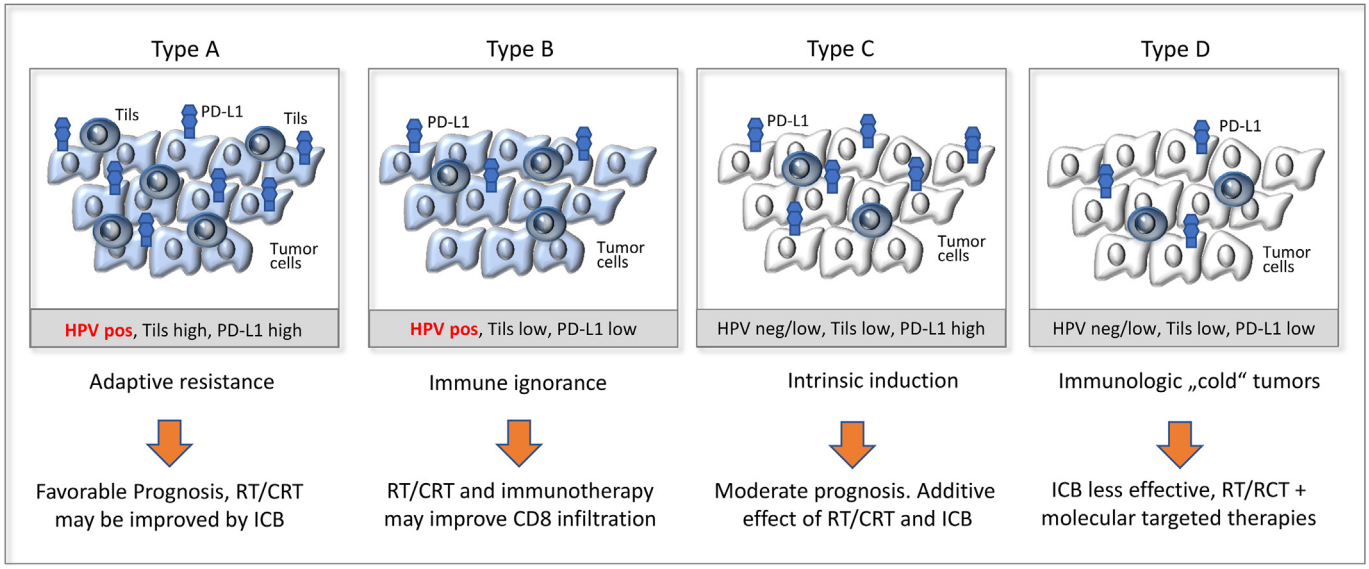

Fig. 2. Simplistic framework of stratifying tumor microenvironment to tailor radiation/radio- chemotherapy (RT/RCT) and immune checkpoint blockade (ICB) strategies. Cancers have been categorized into four different tumor types based on the HPV status and the presence of TILs and PD-L1 expression. These comprise type A (adaptive resistance), type B (immune ignorance), type C (intrinsic induction), and type D (immunologic cold tumors).

8. Conclusions

Preclinical and clinical studies have improved our understanding on the immune profile of a multitude of cancers also in the context of viral infection. Recent research has further granted a clearer perceptive on the mechanisms involved in the viral etiology and immune evasion of tumors and modulation of therapy response by viral factors. In line with that a superior clinical outcome at least in HPV related HNSCC or ASCC following RT or RCT is likely attributable to both, an intrinsic radiation sensitivity and a highly complex interrelationship with a multitude of immune components in the TME. Accordingly, the optimal timing and schedules of combined RT/CRT and immunotherapies [192] in line with alternative approaches like therapeutic vaccination may challenge the design of both future preclinical and clinical studies.

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References

[1] C. de Martel, J. Ferlay, S. Franceschi, J. Vignat, F. Bray, D. Forman, M. Plummer, Global burden of cancers attributable to infections in 2008: a review and synthetic analysis, Lancet Oncol. 13 (2012) 607–615, https://doi.org/10.1016/S1470-2045(12)70137-7 S1470-2045(12)70137-7[pii].

[2] E.A. Mesri, M.A. Feitelson, K. Munger, Human viral oncogenesis: a cancer hallmarks analysis, Cell Host Microbe 15 (2014) 266–282, https://doi.org/10.1016/j.chom.2014.02.011 S1931-3128(14)00069-9[pii].

[3] C. Fakhry, W.H. Westra, S. Li, A. Cmelak, J.A. Ridge, H. Pinto, A. Forastiere, M.L. Gillison, Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial, J. Natl. Cancer Inst. 100 (2008) 261–269, https://doi.org/10.1093/jnci/djn011 (djn011 [pii]).

[4] K.K. Ang, J. Harris, R. Wheeler, R. Weber, D.I. Rosenthal, P.F. Nguyen-Tan, W.H. Westra, C.H. Chung, R.C. Jordan, C. Lu, H. Kim, R. Axelrod, C.C. Silverman, K.P. Redmond, M.L. Gillison, Human papillomavirus and survival of patients with oropharyngeal cancer, N. Engl. J. Med. 363 (2010) 24–35, https://doi.org/10.1056/NEJMoa0912217 (NEJMoa0912217 [pii]).

[5] L.Q.M. Chow, R. Haddad, S. Gupta, A. Mahipal, R. Mehra, M. Tahara, R. Berger, J.P. Eder, B. Burtness, S.H. Lee, B. Keam, H. Kang, K. Muro, J. Weiss, R. Geva, C.C. Lin, H.C. Chung, A. Meister, M. Dolled-Filhart, K. Pathiraja, J.D. Cheng, T.Y. Seiwert, Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort, J. Clin. Oncol. 34 (2016) 3838–3845, https://doi.org/10.1200/JCO.2016.68.1478.

[6] P. Msaouel, E. Massarelli, Immune checkpoint therapy in head and neck cancers, Cancer J. 22 (2016) 108–116, https://doi.org/10.1097/PPO.0000000000000180 00130404-201603000-00008[pii].

[7] P.S. Moore, Y. Chang, Why do viruses cause cancer? Highlights of the first century of human tumour virology, Nat. Rev. Cancer 10 (2010) 878–889, https://doi.org/10.1038/nrc2961 (nrc2961 [pii]).

[8] M. Durst, L. Gissmann, H. Ikenberg, H. Zur Hausen, A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions, Proc. Natl. Acad. Sci. U. S. A. 80 (1983) 3812–3815.

[9] K. Van Doorslaer, Q. Tan, S. Xirasagar, S. Bandaru, V. Gopalan, Y. Mohamoud, Y. Huyen, A.A. McBride, The Papillomavirus Episteme: a central resource for papillomavirus sequence data and analysis, Nucleic Acids Res. 41 (2013) D571–D578, https://doi.org/10.1093/nar/gks984 (gks984 [pii]).

[10] T. Guo, D.W. Eisele, C. Fakhry, The potential impact of prophylactic human papillomavirus vaccination on oropharyngeal cancer, Cancer 122 (2016) 2313–2323, https://doi.org/10.1002/cncr.29992.

[11] C. Lin, S. Franceschi, G.M. Clifford, Human papillomavirus types from infection to cancer in the anus, according to sex and HIV status: a systematic review and meta-analysis, Lancet Infect. Dis. 18 (2018) 198–206 S1473-3099(17)30653-9 [pii] https://doi.org/10.1016/S1473-3099(17)30653-9.

[12] M.E. McLaughlin-Drubin, K. Munger, Oncogenic activities of human papillomaviruses, Virus Res. 143 (2009) 195–208, https://doi.org/10.1016/j.virusres.2009.06.008S0168-1702(09)00221-4[pii].

[13] S. Gupta, P. Kumar, B.C. Das, HPV: Molecular pathways and targets, Curr. Probl. Cancer 42 (2018) 161–174 S0147–0272(18)30077–1 [pii] https://doi.org/10.1016/j.currproblcancer.2018.03.003.

[14] M. Scheffner, B.A. Werness, J.M. Huibregtse, A.J. Levine, P.M. Howley, The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53, Cell 63 (1990) 1129–1136 (0092–8674(90)90409–8 pii).

[15] S. Song, A. Liem, J.A. Miller, P.F. Lambert, Human papillomavirus types 16 E6 and E7 contribute differently to carcinogenesis, Virology 267 (2000) 141–150, https://doi.org/10.1006/viro.1999.0106S0042-6822(99)90106-X[pii].

[16] R.R. Riley, S. Duensing, T. Brake, K. Munger, P.F. Lambert, J.M. Arbeit, Dissection of human papillomavirus E6 and E7 function in transgenic mouse models of cervical carcinogenesis, Cancer Res. 63 (2003) 4862–4871.

[17] C.A. Moody, L.A. Laimins, Human papillomavirus oncoproteins: pathways to transformation, Nat. Rev. Cancer 10 (2010) 550–560, https://doi.org/10.1038/nrc2886 (nrc2886 [pii]).

[18] T.H. Keegan, S.L. Glaser, C.A. Clarke, M.L. Gulley, F.E. Craig, J.A. Digiuseppe, R.F. Dorfman, R.B. Mann, R.F. Ambinder, Epstein-Barr virus as a marker of survival after Hodgkin's lymphoma: a population-based study, J. Clin. Oncol. 23 (2005) 7604–7613, https://doi.org/10.1200/JCO.2005.02.6310.

[19] C.M. Tsang, S.W. Tsao, The role of Epstein-Barr virus infection in the pathogenesis of nasopharyngeal carcinoma, Virol. Sin. 30 (2015) 107–121, https://doi.org/10.1007/s12250-015-3592-5.

[20] J.L. Yates, N. Warren, B. Sugden, Stable replication of plasmids derived from Epstein-Barr virus in various mammalian cells, Nature 313 (1985) 812–815.

[21] M.S. Kang, E. Kieff, Epstein-Barr virus latent genes, Exp. Mol. Med. 47 (2015) e131, , https://doi.org/10.1038/emm.2014.84 (emm201484 [pii]).

[22] H. Zheng, L.L. Li, D.S. Hu, X.Y. Deng, Y. Cao, Role of Epstein-Barr virus encoded latent membrane protein 1 in the carcinogenesis of nasopharyngeal carcinoma, Cell. Mol. Immunol. 4 (2007) 185–196.

[23] L. Ding, L. Li, J. Yang, S. Zhou, W. Li, M. Tang, Y. Shi, W. Yi, Y. Cao, Latent membrane protein 1 encoded by Epstein-Barr virus induces telomerase activity via p16INK4A/Rb/E2F1 and JNK signaling pathways, J. Med. Virol. 79 (2007) 1153–1163, https://doi.org/10.1002/jmv.20896.

[24] M. Wang, F. Yu, W. Wu, Y. Wang, H. Ding, L. Qian, Epstein-Barr virus-encoded microRNAs as regulators in host immune responses, Int. J. Biol. Sci. 14 (2018) 565–576, https://doi.org/10.7150/ijbs.24562 (ijbsv14p0565 [pii]).

[25] M.D. de Jong, G.J. Galasso, B. Gazzard, P.D. Griffiths, D.A. Jabs, E.R. Kern, S.A. Spector, Summary of the II international symposium on cytomegalovirus, Antivir. Res. 39 (1998) 141–162 (S0166354298000448 [pii]).

[26] U.N. Mui, C.T. Haley, S.K. Tyring, Viral oncology: molecular biology and pathogenesis, J. Clin. Med. 6 (2017), https://doi.org/10.3390/jcm6120111jcm6120111 [pii] E111 [pii].

[27] N.A. Krump, J. You, Molecular mechanisms of viral oncogenesis in humans, Nat. Rev. Microbiol. (2018), https://doi.org/10.1038/s41579-018-0064-6[pii].

[28] L. Harkins, A.L. Volk, M. Samanta, I. Mikolaenko, W.J. Britt, K.I. Bland, C.S. Cobbs, Specific localisation of human cytomegalovirus nucleic acids and proteins in human colorectal cancer, Lancet 360 (2002) 1557–1563, https://doi.org/10.1016/S0140-6736(02)11524-8.

[29] M. Samanta, L. Harkins, K. Klemm, W.J. Britt, C.S. Cobbs, High prevalence of human cytomegalovirus in prostatic intraepithelial neoplasia and prostatic carcinoma, J. Urol. 170 (2003) 998–1002, https://doi.org/10.1097/01.ju.0000080263.46164.97S0022-5347(05)63295-8[pii].

[30] C.J. dos Santos, L.M. Stangherlin, E.G. Figueiredo, C. Correa, M.J. Teixeira, M.C. da Silva, High prevalence of HCMV and viral load in tumor tissues and peripheral blood of glioblastoma multiforme patients, J. Med. Virol. 86 (2014) 1953–1961, https://doi.org/10.1002/jmv.23820.

[31] S.G. Babu, A. Pandeya, N. Verma, N. Shukla, R.V. Kumar, S. Saxena, Role of HCMV miR-UL70-3p and miR-UL148D in overcoming the cellular apoptosis, Mol. Cell. Biochem. 393 (2014) 89–98, https://doi.org/10.1007/s11010-014-2049-8.

[32] G.P. Joseph, R. McDermott, M.A. Baryshnikova, C.S. Cobbs, I.V. Ulasov, Cytomegalovirus as an oncomodulatory agent in the progression of glioma, Cancer Lett. 384 (2017) 79–85 S0304–3835(16)30643–7 [pii] https://doi.org/10.1016/j.canlet.2016.10.022.

[33] P. Martinive, F. Defresne, C. Bouzin, J. Saliez, F. Lair, V. Gregoire, C. Michiels, C. Dessy, O. Feron, Preconditioning of the tumor vasculature and tumor cells by intermittent hypoxia: implications for anticancer therapies, Cancer Res. 66 (2006) 11736–11744 66/24/11736 [pii] https://doi.org/10.1158/0008-5472.CAN-06-2056.

[34] G.G. Steel, T.J. McMillan, J.H. Peacock, The 5Rs of radiobiology, Int. J. Radiat. Biol. 56 (1989) 1045–1048 (Q2DLXEDJJ5AAFYVY [pii]).

[35] A.D. Swick, A. Chatterjee, A.M. De Costa, R.J. Kimple, Modulation of therapeutic sensitivity by human papillomavirus, Radiother. Oncol. 116 (2015) 342–345, https://doi.org/10.1016/j.radonc.2015.09.002 (S0167–8140(15)00460–0 pii).

[36] T. Rieckmann, S. Tribius, T.J. Grob, F. Meyer, C.J. Busch, C. Petersen, E. Dikomey, M. Kriegs, HNSCC cell lines positive for HPV and p16 possess higher cellular radiosensitivity due to an impaired DSB repair capacity, Radiother. Oncol. 107 (2013) 242–246, https://doi.org/10.1016/j.radonc.2013.03.013 (S0167–8140(13)00137–0 pii).

[37] A.N. Weaver, T.S. Cooper, M. Rodriguez, H.Q. Trummell, J.A. Bonner, E.L. Rosenthal, E.S. Yang, DNA double strand break repair defect and sensitivity to poly ADP-ribose polymerase (PARP) inhibition in human papillomavirus 16-positive head and neck squamous cell carcinoma, Oncotarget 6 (2015) 26995–27007, https://doi.org/10.18632/oncotarget.4863 (4863 [pii]).

[38] R.J. Kimple, M.A. Smith, G.C. Blitzer, A.D. Torres, J.A. Martin, R.Z. Yang, C.R. Peet, L.D. Lorenz, K.P. Nickel, A.J. Klingelhutz, P.F. Lambert, P.M. Harari, Enhanced radiation sensitivity in HPV-positive head and neck cancer, Cancer Res. 73 (2013) 4791–4800, https://doi.org/10.1158/0008-5472.CAN-13-0587 (0008–5472.CAN-13-0587 [pii]).

[39] I. Fumagalli, D. Dugue, J.E. Bibault, C. Clemenson, M.C. Vozenin, M. Mondini, E. Deutsch, Cytotoxic effect of lapatinib is restricted to human papillomavirus-positive head and neck squamous cell carcinoma cell lines, Onco Targets Ther. 8 (2015) 335–345, https://doi.org/10.2147/OTT.S68235 (ott-8-335 [pii]).

[40] A.K. Gupta, J.H. Lee, W.W. Wilke, H. Quon, G. Smith, A. Maity, J.M. Buatti,

D.R. Spitz, Radiation response in two HPV-infected head-and-neck cancer cell lines in comparison to a non-HPV-infected cell line and relationship to signaling through AKT, Int. J. Radiat. Oncol. Biol. Phys. 74 (2009) 928–933, https://doi.org/10.1016/j.ijrobp.2009.03.004 (S0360–3016(09)00363–0 pii).
[41] T. Iftner, M. Elbel, B. Schopp, T. Hiller, J.I. Loizou, K.W. Caldecott, F. Stubenrauch, Interference of papillomavirus E6 protein with single-strand break repair by interaction with XRCC1, EMBO J. 21 (2002) 4741–4748.
[42] K.H. Shin, J.H. Ahn, M.K. Kang, P.K. Lim, F.K. Yip, M.A. Baluda, N.H. Park, HPV-16 E6 oncoprotein impairs the fidelity of DNA end-joining via p53-dependent and -independent pathways, Int. J. Oncol. 28 (2006) 209–215.
[43] R. Dok, P. Kalev, E.J. Van Limbergen, L.A. Asbagh, I. Vazquez, E. Hauben, A. Sablina, S. Nuyts, p16INK4a impairs homologous recombination-mediated DNA repair in human papillomavirus-positive head and neck tumors, Cancer Res. 74 (2014) 1739–1751, https://doi.org/10.1158/0008-5472.CAN-13-2479 (0008–5472.CAN-13-2479 pii).
[44] L. Wang, P. Zhang, D.P. Molkentine, C. Chen, J.M. Molkentine, H. Piao, U. Raju, J. Zhang, D.R. Valdecanas, R.C. Tailor, H.D. Thames, T.A. Buchholz, J. Chen, L. Ma, K.A. Mason, K.K. Ang, R.E. Meyn, H.D. Skinner, TRIP12 as a mediator of human papillomavirus/p16-related radiation enhancement effects, Oncogene 36 (2017) 820–828, https://doi.org/10.1038/onc.2016.250 (onc2016250 [pii]).
[45] Q. Liu, L. Ma, T. Jones, L. Palomero, M.A. Pujana, H. Martinez-Ruiz, P.K. Ha, J. Murnane, I. Cuartas, J. Seoane, M. Baumann, A. Linge, M.H. Barcellos-Hoff, Subjugation of TGFbeta signaling by human Papilloma virus in head and neck squamous cell carcinoma shifts DNA repair from homologous recombination to alternative end-joining, Clin. Cancer Res. (2018), https://doi.org/10.1158/1078-0432.CCR-18-1346 clincanres.1346.2018 [pii]. (1078–0432.CCR-18-1346 [pii]).
[46] E. Gubanova, B. Brown, S.V. Ivanov, T. Helleday, G.B. Mills, W.G. Yarbrough, N. Issaeva, Downregulation of SMG-1 in HPV-positive head and neck squamous cell carcinoma due to promoter hypermethylation correlates with improved survival, Clin. Cancer Res. 18 (2012) 1257–1267, https://doi.org/10.1158/1078-0432.CCR-11-2058 (1078–0432.CCR-11-2058 [pii]).
[47] T.L. DeWeese, J.C. Walsh, L.E. Dillehay, T.D. Kessis, L. Hedrick, K.R. Cho, W.G. Nelson, Human papillomavirus E6 and E7 oncoproteins alter cell cycle progression but not radiosensitivity of carcinoma cells treated with low-dose-rate radiation, Int. J. Radiat. Oncol. Biol. Phys. 37 (1997) 145–154 (S0360301696004488 [pii]).
[48] M.C. Kamradt, N. Mohideen, E. Krueger, S. Walter, A.T. Vaughan, Inhibition of radiation-induced apoptosis by dexamethasone in cervical carcinoma cell lines depends upon increased HPV E6/E7, Br. J. Cancer 82 (2000) 1709–1716 S0007092000911145 [pii] https://doi.org/10.1054/bjoc.2000.1114.
[49] J. Lu, M. Tang, H. Li, Z. Xu, X. Weng, J. Li, X. Yu, L. Zhao, H. Liu, Y. Hu, Z. Tan, L. Yang, M. Zhong, J. Zhou, J. Fan, A.M. Bode, W. Yi, J. Gao, L. Sun, Y. Cao, EBV-LMP1 suppresses the DNA damage response through DNA-PK/AMPK signaling to promote radioresistance in nasopharyngeal carcinoma, Cancer Lett. 380 (2016) 191–200, https://doi.org/10.1016/j.canlet.2016.05.032S0304-3835(16)30345-7[pii].
[50] B. Gruhne, R. Sompallae, M.G. Masucci, Three Epstein-Barr virus latency proteins independently promote genomic instability by inducing DNA damage, inhibiting DNA repair and inactivating cell cycle checkpoints, Oncogene 28 (2009) 3997–4008, https://doi.org/10.1038/onc.2009.258 (onc2009258 [pii]).
[51] L. Xiao, Z.Y. Hu, X. Dong, Z. Tan, W. Li, M. Tang, L. Chen, L. Yang, Y. Tao, Y. Jiang, J. Li, B. Yi, B. Li, S. Fan, S. You, X. Deng, F. Hu, L. Feng, A.M. Bode, Z. Dong, L.Q. Sun, Y. Cao, Targeting Epstein-Barr virus oncoprotein LMP1-mediated glycolysis sensitizes nasopharyngeal carcinoma to radiation therapy, Oncogene 33 (2014) 4568–4578, https://doi.org/10.1038/onc.2014.32.
[52] L. Yang, L. Liu, Z. Xu, W. Liao, D. Feng, X. Dong, S. Xu, L. Xiao, J. Lu, X. Luo, M. Tang, A.M. Bode, Z. Dong, L. Sun, Y. Cao, EBV-LMP1 targeted DNAzyme enhances radiosensitivity by inhibiting tumor angiogenesis via the JNKs/HIF-1 pathway in nasopharyngeal carcinoma, Oncotarget 6 (2015) 5804–5817 3331 [pii] 10.18632/oncotarget.3331.
[53] X. Ma, L. Yang, L. Xiao, M. Tang, L. Liu, Z. Li, M. Deng, L. Sun, Y. Cao, Down-regulation of EBV-LMP1 radio-sensitizes nasal pharyngeal carcinoma cells via NF-kappaB regulated ATM expression, PLoS ONE 6 (2011) e24647, , https://doi.org/10.1371/journal.pone.0024647 (PONE-D-11-03325 [pii]).
[54] C.F. Yang, L.X. Peng, T.J. Huang, G.D. Yang, Q.Q. Chu, Y.Y. Liang, X. Cao, P. Xie, L.S. Zheng, H.B. Huang, M.D. Cai, J.L. Huang, R.Y. Liu, Z.Y. Zhu, C.N. Qian, B.J. Huang, Cancer stem-like cell characteristics induced by EB virus-encoded LMP1 contribute to radioresistance in nasopharyngeal carcinoma by suppressing the p53-mediated apoptosis pathway, Cancer Lett. 344 (2014) 260–271, https://doi.org/10.1016/j.canlet.2013.11.006 (S0304–3835(13)00808–2 [pii]).
[55] F. Yang, Q. Liu, C.M. Hu, Epstein-Barr virus-encoded LMP1 increases miR-155 expression, which promotes radioresistance of nasopharyngeal carcinoma via suppressing UBQLN1, Eur. Rev. Med. Pharmacol. Sci. 19 (2015) 4507–4515 (9933 [pii]).
[56] W. Gao, Z.H. Li, S. Chen, J.Y. Chan, M. Yin, M.J. Zhang, T.S. Wong, Epstein-Barr virus encoded microRNA BART7 regulates radiation sensitivity of nasopharyngeal carcinoma, Oncotarget 8 (2017) 20297–20308, https://doi.org/10.18632/oncotarget.15526 (15526 [pii]).
[57] S. Henderson, D. Huen, M. Rowe, C. Dawson, G. Johnson, A. Rickinson, Epstein-Barr virus-coded BHRF1 protein, a viral homologue of Bcl-2, protects human B cells from programmed cell death, Proc. Natl. Acad. Sci. U. S. A. 90 (1993) 8479–8483.
[58] E.A. Rourke, M.S. Lopez, C.M. Monroy, M.E. Scheurer, C.J. Etzel, T. Albrecht, M.L. Bondy, R.A. El-Zein, Modulation of radiation-induced genetic damage by HCMV in peripheral blood lymphocytes from a brain tumor case-control study, Cancers (Basel) 2 (2010) 420–435, https://doi.org/10.3390/cancers2020420 (cancers2020420 [pii]).
[59] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674, https://doi.org/10.1016/j.cell.2011.02.013 (S0092–8674(11)00127–9 pii).
[60] S.S. McAllister, R.A. Weinberg, The tumour-induced systemic environment as a critical regulator of cancer progression and metastasis, Nat. Cell Biol. 16 (2014) 717–727, https://doi.org/10.1038/ncb3015 (ncb3015 [pii]).
[61] W.H. Fridman, F. Pages, C. Sautes-Fridman, J. Galon, The immune contexture in human tumours: impact on clinical outcome, Nat. Rev. Cancer 12 (2012) 298–306, https://doi.org/10.1038/nrc3245.
[62] N. Bhardwaj, Harnessing the immune system to treat cancer, J. Clin. Invest. 117 (2007) 1130–1136, https://doi.org/10.1172/JCI32136.
[63] G.P. Dunn, A.T. Bruce, H. Ikeda, L.J. Old, R.D. Schreiber, Cancer immunoediting: from immunosurveillance to tumor escape, Nat. Immunol. 3 (2002) 991–998, https://doi.org/10.1038/ni1102-991 (ni1102-991 [pii]).
[64] A. Mantovani, A. Sica, P. Allavena, C. Garlanda, M. Locati, Tumor-associated macrophages and the related myeloid-derived suppressor cells as a paradigm of the diversity of macrophage activation, Hum. Immunol. 70 (2009) 325–330, https://doi.org/10.1016/j.humimm.2009.02.008 (S0198–8859(09)00048–2 [pii]).
[65] F. Veglia, M. Perego, D. Gabrilovich, Myeloid-derived suppressor cells coming of age, Nat. Immunol. 19 (2018) 108–119, https://doi.org/10.1038/s41590-017-0022-x ([pii]).
[66] M. Otsuji, Y. Kimura, T. Aoe, Y. Okamoto, T. Saito, Oxidative stress by tumor-derived macrophages suppresses the expression of CD3 zeta chain of T-cell receptor complex and antigen-specific T-cell responses, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 13119–13124.
[67] T.N. Schumacher, R.D. Schreiber, Neoantigens in cancer immunotherapy, Science 348 (2015) 69–74, https://doi.org/10.1126/science.aaa4971 348/6230/69 ([pii]).
[68] A.K. Grabowska, A.B. Riemer, The invisible enemy - how human papillomaviruses avoid recognition and clearance by the host immune system, Open Virol. J. 6 (2012) 249–256, https://doi.org/10.2174/1874357901206010249 (TOVJ-6-249 [pii]).
[69] S.E. Jackson, A. Redeker, R. Arens, D. van Baarle, S.P.H. van den Berg, C.A. Benedict, L. Cicin-Sain, A.B. Hill, M.R. Wills, CMV immune evasion and manipulation of the immune system with aging, Geroscience 39 (2017) 273–291, https://doi.org/10.1007/s11357-017-9986-6.
[70] A. Steinbach, A.B. Riemer, Immune evasion mechanisms of human papillomavirus: an update, Int. J. Cancer 142 (2018) 224–229, https://doi.org/10.1002/ijc.31027.
[71] A.A. McBride, A. Warburton, The role of integration in oncogenic progression of HPV-associated cancers, PLoS Pathog. 13 (2017) e1006211, , https://doi.org/10.1371/journal.ppat.1006211.
[72] G.H. Ashrafi, M.R. Haghshenas, B. Marchetti, P.M. O'Brien, M.S. Campo, E5 protein of human papillomavirus type 16 selectively downregulates surface HLA class I, Int. J. Cancer 113 (2005) 276–283, https://doi.org/10.1002/ijc.20558.
[73] M. Bauer, H. Wagner, G.B. Lipford, HPV type 16 protein E7 HLA-A2 binding peptides are immunogenic but not processed and presented, Immunol. Lett. 71 (2000) 55–59 (S0165–2478(99)00170–4 [pii]).
[74] C. Powers, V. DeFilippis, D. Malouli, K. Fruh, Cytomegalovirus immune evasion, Curr. Top. Microbiol. Immunol. 325 (2008) 333–359.
[75] N.A. Lemmermann, A. Fink, J. Podlech, S. Ebert, V. Wilhelmi, V. Bohm, R. Holtappels, M.J. Reddehase, Murine cytomegalovirus immune evasion proteins operative in the MHC class I pathway of antigen processing and presentation: state of knowledge, revisions, and questions, Med. Microbiol. Immunol. 201 (2012) 497–512, https://doi.org/10.1007/s00430-012-0257-y.
[76] Y. Yin, B. Manoury, R. Fahraeus, Self-inhibition of synthesis and antigen presentation by Epstein-Barr virus-encoded EBNA1, Science 301 (2003) 1371–1374, https://doi.org/10.1126/science.1088902 301/5638/1371 (pii).
[77] W.A. Burgers, L. Blanchon, S. Pradhan, Y. de Launoit, T. Kouzarides, F. Fuks, Viral oncoproteins target the DNA methyltransferases, Oncogene 26 (2007) 1650–1655, https://doi.org/10.1038/sj.onc.1209950.
[78] L. Cicchini, J.A. Westrich, T. Xu, D.W. Vermeer, J.N. Berger, E.T. Clambey, D. Lee, J.I. Song, P.F. Lambert, R.O. Greer, J.H. Lee, D. Pyeon, Suppression of antitumor immune responses by human papillomavirus through epigenetic downregulation of CXCL14, MBio 7 (2016), https://doi.org/10.1128/mBio.00270-16.
[79] N. Munoz, X. Castellsague, A.B. de Gonzalez, L. Gissmann, Chapter 1: HPV in the etiology of human cancer, Vaccine 24 (Suppl. 3) (2006), https://doi.org/10.1016/j.vaccine.2006.05.115 S3/1–10, S0264-410X(06)00591–3 [pii].
[80] L. Pacini, C. Savini, R. Ghittoni, D. Saidj, J. Lamartine, U.A. Hasan, R. Accardi, M. Tommasino, Downregulation of Toll-like receptor 9 expression by beta human papillomavirus 38 and implications for cell cycle control, J. Virol. 89 (2015) 11396–11405, https://doi.org/10.1128/JVI.02151-15 (JVI.02151-15 [pii]).
[81] C. Martinez-Campos, A.I. Burguete-Garcia, V. Madrid-Marina, Role of TLR9 in oncogenic virus-produced cancer, Viral Immunol. 30 (2017) 98–105, https://doi.org/10.1089/vim.2016.0103.
[82] P. Barnard, E. Payne, N.A. McMillan, The human papillomavirus E7 protein is able to inhibit the antiviral and anti-growth functions of interferon-alpha, Virology 277 (2000) 411–419, https://doi.org/10.1006/viro.2000.0584 (S0042-6822(00)90584–1 [pii]).
[83] J.S. Park, E.J. Kim, H.J. Kwon, E.S. Hwang, S.E. Namkoong, S.J. Um, Inactivation of interferon regulatory factor-1 tumor suppressor protein by HPV E7 oncoprotein. Implication for the E7-mediated immune evasion mechanism in cervical carcinogenesis, J. Biol. Chem. 275 (2000) 6764–6769.
[84] L. Lau, E.E. Gray, R.L. Brunette, D.B. Stetson, DNA tumor virus oncogenes antagonize the cGAS-STING DNA-sensing pathway, Science 350 (2015) 568–571,

https://doi.org/10.1126/science.aab3291 (science.aab3291 [pii]).
[85] N. Sunthamala, F. Thierry, S. Teissier, C. Pientong, B. Kongyingyoes, T. Tangsiriwatthana, U. Sangkomkamhang, T. Ekalaksananan, E2 proteins of high risk human papillomaviruses down-modulate STING and IFN-kappa transcription in keratinocytes, PLoS ONE 9 (2014) e91473, , https://doi.org/10.1371/journal.pone.0091473 (PONE-D-13-48420 [pii]).
[86] J. Wu, L. Sun, X. Chen, F. Du, H. Shi, C. Chen, Z.J. Chen, Cyclic GMP-AMP is an endogenous second messenger in innate immune signaling by cytosolic DNA, Science 339 (2013) 826–830, https://doi.org/10.1126/science.1229963.
[87] X. Cai, Y.H. Chiu, Z.J. Chen, The cGAS-cGAMP-STING pathway of cytosolic DNA sensing and signaling, Mol. Cell 54 (2014) 289–296, https://doi.org/10.1016/j.molcel.2014.03.040 (S1097–2765(14)00273–1 [pii]).
[88] L. Deng, H. Liang, M. Xu, X. Yang, B. Burnette, A. Arina, X.D. Li, H. Mauceri, M. Beckett, T. Darga, X. Huang, T.F. Gajewski, Z.J. Chen, Y.X. Fu, R.R. Weichselbaum, STING-dependent cytosolic DNA sensing promotes radiation-induced type I interferon-dependent antitumor immunity in immunogenic tumors, Immunity 41 (2014) 843–852, https://doi.org/10.1016/j.immuni.2014.10.019.
[89] G. Del Prete, The concept of type-1 and type-2 helper T cells and their cytokines in humans, Int. Rev. Immunol. 16 (1998) 427–455.
[90] D. Song, H. Li, J. Dai, Effect of human papillomavirus infection on the immune system and its role in the course of cervical cancer, Oncol. Lett. 10 (2015) 600–606, https://doi.org/10.3892/ol.2015.3295 (OL-0-0-3295 [pii]).
[91] S.L. Topalian, C.G. Drake, D.M. Pardoll, Immune checkpoint blockade: a common denominator approach to cancer therapy, Cancer Cell 27 (2015) 450–461, https://doi.org/10.1016/j.ccell.2015.03.001 (S1535–6108(15)00089–6 [pii]).
[92] S.L. Topalian, J.M. Taube, R.A. Anders, D.M. Pardoll, Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy, Nat. Rev. Cancer 16 (2016) 275–287, https://doi.org/10.1038/nrc.2016.36 (nrc.2016.36 [pii]).
[93] C. Liu, J. Lu, H. Tian, W. Du, L. Zhao, J. Feng, D. Yuan, Z. Li, Increased expression of PDL1 by the human papillomavirus 16 E7 oncoprotein inhibits anticancer immunity, Mol. Med. Rep. 15 (2017) 1063–1070, https://doi.org/10.3892/mmr.2017.6102.
[95] A.D. Beaulieu, R. Paquin, J. Gosselin, Epstein-Barr virus modulates de novo protein synthesis in human neutrophils, Blood 86 (1995) 2789–2798.
[96] S.R. McColl, C.J. Roberge, B. Larochelle, J. Gosselin, EBV induces the production and release of IL-8 and macrophage inflammatory protein-1 alpha in human neutrophils, J. Immunol. 159 (1997) 6164–6168.
[97] B. Larochelle, L. Flamand, P. Gourde, D. Beauchamp, J. Gosselin, Epstein-Barr virus infects and induces apoptosis in human neutrophils, Blood 92 (1998) 291–299.
[98] M. Tardif, M. Savard, L. Flamand, J. Gosselin, Impaired protein kinase C activation/translocation in Epstein-Barr virus-infected monocytes, J. Biol. Chem. 277 (2002) 24148–24154, https://doi.org/10.1074/jbc.M109036200 (M109036200 [pii]).
[99] J. Gosselin, J. Menezes, M. D'Addario, J. Hiscott, L. Flamand, G. Lamoureux, D. Oth, Inhibition of tumor necrosis factor-alpha transcription by Epstein-Barr virus, Eur. J. Immunol. 21 (1991) 203–208, https://doi.org/10.1002/eji.1830210130.
[100] N.A. Marshall, M.A. Vickers, R.N. Barker, Regulatory T cells secreting IL-10 dominate the immune response to EBV latent membrane protein 1, J. Immunol. 170 (2003) 6183–6189.
[101] M. Albanese, T. Tagawa, M. Bouvet, L. Maliqi, D. Lutter, J. Hoser, M. Hastreiter, M. Hayes, B. Sugden, L. Martin, A. Moosmann, W. Hammerschmidt, Epstein-Barr virus microRNAs reduce immune surveillance by virus-specific CD8+ T cells, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) E6467–E6475 1605884113 [pii] https://doi.org/10.1073/pnas.1605884113.
[102] S.Y. Teow, K. Liew, A.S. Khoo, S.C. Peh, Pathogenic role of exosomes in Epstein-Barr Virus (EBV)-associated cancers, Int. J. Biol. Sci. 13 (2017) 1276–1286, https://doi.org/10.7150/ijbs.19531 (ijbsv13p1276 [pii]).
[103] L. Amsler, M. Verweij, V.R. DeFilippis, The tiers and dimensions of evasion of the type I interferon response by human cytomegalovirus, J. Mol. Biol. 425 (2013) 4857–4871, https://doi.org/10.1016/j.jmb.2013.08.023 (S0022–2836(13)00556–1 [pii]).
[104] W. Brune, C.E. Andoniou, Die another day: inhibition of cell death pathways by cytomegalovirus, Viruses 9 (2017), https://doi.org/10.3390/v9090249 E249 [pii]. (v9090249 [pii]).
[105] D. Piedade, J.M. Azevedo-Pereira, The role of microRNAs in the pathogenesis of herpesvirus infection, Viruses 8 (2016), https://doi.org/10.3390/v8060156 E156 [pii]. (v8060156 [pii]).
[106] B.P. McSharry, S. Avdic, B. Slobedman, Human cytomegalovirus encoded homologs of cytokines, chemokines and their receptors: roles in immunomodulation, Viruses 4 (2012) 2448–2470, https://doi.org/10.3390/v4112448 (v4112448 [pii]).
[107] C. Jenkins, W. Garcia, M.J. Godwin, J.V. Spencer, J.L. Stern, A. Abendroth, B. Slobedman, Immunomodulatory properties of a viral homolog of human interleukin-10 expressed by human cytomegalovirus during the latent phase of infection, J. Virol. 82 (2008) 3736–3750, https://doi.org/10.1128/JVI.02173-07 (JVI.02173-07 [pii]).
[108] A.R. Kreimer, G.M. Clifford, P. Boyle, S. Franceschi, Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review, Cancer Epidemiol. Biomark. Prev. 14 (2005) 467–475 14/2/467 [pii] https://doi.org/10.1158/1055-9965.EPI-04-0551.
[109] A.P. Stein, S. Saha, M. Yu, R.J. Kimple, P.F. Lambert, Prevalence of human papillomavirus in oropharyngeal squamous cell carcinoma in the United States across time, Chem. Res. Toxicol. 27 (2014) 462–469, https://doi.org/10.1021/tx500034c.
[110] K.K. Ang, E.M. Sturgis, Human papillomavirus as a marker of the natural history and response to therapy of head and neck squamous cell carcinoma, Semin. Radiat. Oncol. 22 (2012) 128–142, https://doi.org/10.1016/j.semradonc.2011.12.004 (S1053–4296(11)00138-X [pii]).
[111] F. Lohaus, A. Linge, I. Tinhofer, V. Budach, E. Gkika, M. Stuschke, P. Balermpas, C. Rodel, M. Avlar, A.L. Grosu, A. Abdollahi, J. Debus, C. Bayer, C. Belka, S. Pigorsch, S.E. Combs, D. Monnich, D. Zips, C. von Neubeck, G.B. Baretton, S. Lock, H.D. Thames, M. Krause, M. Baumann, R.O.G. Dktk, HPV16 DNA status is a strong prognosticator of loco-regional control after postoperative radiochemotherapy of locally advanced oropharyngeal carcinoma: results from a multicentre explorative study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG), Radiother Oncol. 113 (2014) 317–323, https://doi.org/10.1016/j.radonc.2014.11.011.
[112] C.C. Ragin, E. Taioli, Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis, Int. J. Cancer 121 (2007) 1813–1820, https://doi.org/10.1002/ijc.22851.
[113] A.M. Chen, C. Felix, P.C. Wang, S. Hsu, V. Basehart, J. Garst, P. Beron, D. Wong, M.H. Rosove, S. Rao, H. Melanson, E. Kim, D. Palmer, L. Qi, K. Kelly, M.L. Steinberg, P.A. Kupelian, M.E. Daly, Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: a single-arm, phase 2 study, Lancet Oncol. 18 (2017) 803–811 S1470–2045(17)30246–2 [pii] https://doi.org/10.1016/S1470-2045(17)30246-2.
[114] G.C. Blitzer, M.A. Smith, S.L. Harris, R.J. Kimple, Review of the clinical and biologic aspects of human papillomavirus-positive squamous cell carcinomas of the head and neck, Int. J. Radiat. Oncol. Biol. Phys. 88 (2014) 761–770, https://doi.org/10.1016/j.ijrobp.2013.08.029 (S0360–3016(13)03035–6 [pii]).
[115] L. Masterson, M. Lechner, S. Loewenbein, H. Mohammed, C. Davies-Husband, T. Fenton, H. Sudhoff, P. Jani, P. Goon, J. Sterling, CD8(+) T cell response to human papillomavirus 16 E7 is able to predict survival outcome in oropharyngeal cancer, Eur. J. Cancer 67 (2016) 141–151 S0959–8049(16)32385–1 [pii] https://doi.org/10.1016/j.ejca.2016.08.012.
[116] M.R. Posner, J.H. Lorch, O. Goloubeva, M. Tan, L.M. Schumaker, N.J. Sarlis, R.I. Haddad, K.J. Cullen, Survival and human papillomavirus in oropharynx cancer in TAX 324: a subset analysis from an international phase III trial, Ann. Oncol. 22 (2011) 1071–1077, https://doi.org/10.1093/annonc/mdr006 (mdr006 [pii]).
[117] G.R. Williams, Q.L. Lu, S.B. Love, I.C. Talbot, J.M. Northover, Properties of HPV-positive and HPV-negative anal carcinomas, J. Pathol. 180 (1996) 378–382 ([pii] 10.1002/(SICI)1096-9896(199612)180:4 < 378::AID-PATH697 > 3.0.CO;2-H).
[118] S.A. Koerber, C. Schoneweg, A. Slynko, D. Krug, M.F. Haefner, K. Herfarth, J. Debus, F. Sterzing, M. von Knebel Doeberitz, E.S. Prigge, M. Reuschenbach, Influence of human papillomavirus and p16(INK4a) on treatment outcome of patients with anal cancer, Radiother. Oncol. 113 (2014) 331–336, https://doi.org/10.1016/j.radonc.2014.11.013 (S0167–8140(14)00492–7 [pii]).
[119] H.Y. Yhim, N.R. Lee, E.K. Song, J.Y. Kwak, S.T. Lee, J.H. Kim, J.S. Kim, H.S. Park, I.J. Chung, H.J. Shim, J.E. Hwang, H.R. Kim, T.K. Nam, M.R. Park, H. Shim, H.S. Kim, C.Y. Yim, The prognostic significance of tumor human papillomavirus status for patients with anal squamous cell carcinoma treated with combined chemoradiotherapy, Int. J. Cancer 129 (2011) 1752–1760, https://doi.org/10.1002/ijc.25825.
[120] E. Serup-Hansen, D. Linnemann, W. Skovrider-Ruminski, E. Hogdall, P.F. Geertsen, H. Havsteen, Human papillomavirus genotyping and p16 expression as prognostic factors for patients with American Joint Committee on Cancer stages I to III carcinoma of the anal canal, J. Clin. Oncol. 32 (2014) 1812–1817, https://doi.org/10.1200/JCO.2013.52.3464 (JCO.2013.52.3464 [pii]).
[121] Z. Yuan, A.O. Naghavi, D. Tang, Y. Kim, K.A. Ahmed, J. Dhillon, A.R. Giuliano, P.E. Spiess, P.A. Johnstone, The relationship between HPV status and chemoradiotherapy in the locoregional control of penile cancer, World J. Urol. 36 (2018) 1431–1440, https://doi.org/10.1007/s00345-018-2280-0 ([pii]).
[122] K. Wakeham, K. Kavanagh, K. Cuschieri, D. Millan, K.G. Pollock, S. Bell, K. Burton, N.S. Reed, S.V. Graham, HPV status and favourable outcome in vulvar squamous cancer, Int. J. Cancer 140 (2017) 1134–1146, https://doi.org/10.1002/ijc.30523.
[123] F. Rodel, U. Wieland, I. Fraunholz, J. Kitz, M. Rave-Frank, H.A. Wolff, C. Weiss, R. Wirtz, P. Balermpas, E. Fokas, C. Rodel, Human papillomavirus DNA load and p16INK4a expression predict for local control in patients with anal squamous cell carcinoma treated with chemoradiotherapy, Int. J. Cancer 136 (2015) 278–288, https://doi.org/10.1002/ijc.28979.
[124] I. Baricevic, X. He, B. Chakrabarty, A.W. Oliver, C. Bailey, J. Summers, L. Hampson, I. Hampson, D.C. Gilbert, A.G. Renehan, High-sensitivity human Papilloma virus genotyping reveals near universal positivity in anal squamous cell carcinoma: different implications for vaccine prevention and prognosis, Eur. J. Cancer 51 (2015) 776–785, https://doi.org/10.1016/j.ejca.2015.01.058 (S0959–8049(15)00102–1 [pii]).
[125] U. Mahantshetty, T. Teni, P. Naga, C. Hotwani, S. Umesh, S. Kannan, V. Hande, S. Pawar, R. Engineer, S. Chopra, K. Deodhar, A. Maheshwari, L. Gurram, S. Gupta, S.K. Shrivastava, Impact of HPV 16/18 infection on clinical outcomes in locally advanced cervical cancers treated with radical radio (chemo) therapy - A prospective observational study, Gynecol. Oncol. 148 (2018) 299–304 S0090–8258(17)31544–5 [pii] https://doi.org/10.1016/j.ygyno.2017.11.034.
[126] J.A. Ajani, X. Wang, J.G. Izzo, C.H. Crane, C. Eng, J.M. Skibber, P. Das, A. Rashid, Molecular biomarkers correlate with disease-free survival in patients with anal canal carcinoma treated with chemoradiation, Dig. Dis. Sci. 55 (2010) 1098–1105, https://doi.org/10.1007/s10620-009-0812-6.
[127] O. Bruland, O. Fluge, H. Immervoll, L. Balteskard, M. Myklebust, A. Skarstein, O. Dahl, Gene expression reveals two distinct groups of anal carcinomas with clinical implications, Br. J. Cancer 98 (2008) 1264–1273, https://doi.org/10.

1038/sj.bjc.6604285 (6604285 [pii]).
[128] G.B. Roldan Urgoiti, K. Gustafson, A.C. Klimowicz, S.K. Petrillo, A.M. Magliocco, C.M. Doll, The prognostic value of HPV status and p16 expression in patients with carcinoma of the anal canal, PLoS ONE 9 (2014) e108790, , https://doi.org/10.1371/journal.pone.0108790 (PONE-D-14-18499 [pii]).
[129] D. Meulendijks, N.B. Tomasoa, L. Dewit, P.H. Smits, R. Bakker, M.L. van Velthuysen, E.H. Rosenberg, J.H. Beijnen, J.H. Schellens, A. Cats, HPV-negative squamous cell carcinoma of the anal canal is unresponsive to standard treatment and frequently carries disruptive mutations in TP53, Br. J. Cancer 112 (2015) 1358–1366, https://doi.org/10.1038/bjc.2015.20 (bjc201520 [pii]).
[130] S. Mai, G. Welzel, M. Ottstadt, F. Lohr, S. Severa, E.S. Prigge, N. Wentzensen, M.J. Trunk, F. Wenz, M. von Knebel-Doeberitz, M. Reuschenbach, Prognostic relevance of HPV infection and p16 overexpression in squamous cell anal cancer, Int. J. Radiat. Oncol. Biol. Phys. 93 (2015) 819–827, https://doi.org/10.1016/j.ijrobp.2015.08.004 (S0360–3016(15)03117-X [pii]).
[131] I.H. Frazer, Interaction of human papillomaviruses with the host immune system: a well evolved relationship, Virology 384 (2009) 410–414, https://doi.org/10.1016/j.virol.2008.10.004 (S0042–6822(08)00662–4 [pii]).
[132] A.R. Kreimer, P. Brennan, K.A. Lang Kuhs, T. Waterboer, G. Clifford, S. Franceschi, A. Michel, M. Willhauck-Fleckenstein, E. Riboli, X. Castellsague, A. Hildesheim, R.T. Fortner, R. Kaaks, D. Palli, I. Ljuslinder, S. Panico, F. Clavel-Chapelon, M.C. Boutron-Ruault, S. Mesrine, A. Trichopoulou, P. Lagiou, D. Trichopoulos, P.H. Peeters, A.J. Cross, H.B. Bueno-de-Mesquita, P. Vineis, N. Larranaga, V. Pala, M.J. Sanchez, C. Navarro, A. Barricarte, R. Tumino, K.T. Khaw, N. Wareham, H. Boeing, A. Steffen, R.C. Travis, J.R. Quiros, E. Weiderpass, M. Pawlita, M. Johansson, Human papillomavirus antibodies and future risk of anogenital cancer: a nested case-control study in the European prospective investigation into cancer and nutrition study, J. Clin. Oncol. 33 (2015) 877–884, https://doi.org/10.1200/JCO.2014.57.8435 (JCO.2014.57.8435 [pii]).
[133] A.R. Kreimer, M. Johansson, T. Waterboer, R. Kaaks, J. Chang-Claude, D. Drogen, A. Tjonneland, K. Overvad, J.R. Quiros, C.A. Gonzalez, M.J. Sanchez, N. Larranaga, C. Navarro, A. Barricarte, R.C. Travis, K.T. Khaw, N. Wareham, A. Trichopoulou, P. Lagiou, D. Trichopoulos, P.H. Peeters, S. Panico, G. Masala, S. Grioni, R. Tumino, P. Vineis, H.B. Bueno-de-Mesquita, G. Laurell, G. Hallmans, J. Manjer, J. Ekstrom, G. Skeie, E. Lund, E. Weiderpass, P. Ferrari, G. Byrnes, I. Romieu, E. Riboli, A. Hildesheim, H. Boeing, M. Pawlita, P. Brennan, Evaluation of human papillomavirus antibodies and risk of subsequent head and neck cancer, J. Clin. Oncol. 31 (2013) 2708–2715, https://doi.org/10.1200/JCO.2012.47.2738 (JCO.2012.47.2738 [pii]).
[134] D. Holzinger, G. Wichmann, L. Baboci, A. Michel, D. Hofler, M. Wiesenfarth, L. Schroeder, P. Boscolo-Rizzo, C. Herold-Mende, G. Dyckhoff, A. Boehm, A. Del Mistro, F.X. Bosch, A. Dietz, M. Pawlita, T. Waterboer, Sensitivity and specificity of antibodies against HPV16 E6 and other early proteins for the detection of HPV16-driven oropharyngeal squamous cell carcinoma, Int. J. Cancer 140 (2017) 2748–2757, https://doi.org/10.1002/ijc.30697.
[135] G.J. Hanna, V. Sridharan, D.N. Margalit, S.K. La Follette, N.G. Chau, G. Rabinowits, J.H. Lorch, R.I. Haddad, R.B. Tishler, K.S. Anderson, J.D. Schoenfeld, Salivary and serum HPV antibody levels before and after definitive treatment in patients with oropharyngeal squamous cell carcinoma, Cancer Biomark 19 (2017) 129–136, https://doi.org/10.3233/CBM-160071 (CBM160071 [pii]).
[136] C. Fakhry, J.R. Qualliotine, Z. Zhang, N. Agrawal, D.A. Gaykalova, J.A. Bishop, R.M. Subramaniam, W.M. Koch, C.H. Chung, D.W. Eisele, J. Califano, R.P. Viscidi, Serum antibodies to HPV16 early proteins warrant investigation as potential biomarkers for risk stratification and recurrence of HPV-associated oropharyngeal cancer, Cancer Prev. Res. (Phila.) 9 (2016) 135–141, https://doi.org/10.1158/1940-6207.CAPR-15-0299 (1940–6207.CAPR-15-0299 [pii]).
[137] K.A. Lang Kuhs, A.R. Kreimer, S. Trivedi, D. Holzinger, M. Pawlita, R.M. Pfeiffer, S.P. Gibson, N.C. Schmitt, A. Hildesheim, T. Waterboer, R.L. Ferris, Human papillomavirus 16 E6 antibodies are sensitive for human papillomavirus-driven oropharyngeal cancer and are associated with recurrence, Cancer 123 (2017) 4382–4390, https://doi.org/10.1002/cncr.30966.
[138] K.R. Dahlstrom, K.S. Anderson, J.N. Cheng, D. Chowell, G. Li, M. Posner, E.M. Sturgis, HPV serum antibodies as predictors of survival and disease progression in patients with HPV-positive squamous cell carcinoma of the oropharynx, Clin. Cancer Res. 21 (2015) 2861–2869, https://doi.org/10.1158/1078-0432.CCR-14-3323 (21/12/2861 [pii]).
[139] A.H. Hopman, F. Smedts, W. Dignef, M. Ummelen, G. Sonke, M. Mravunac, G.P. Vooijs, E.J. Speel, F.C. Ramaekers, Transition of high-grade cervical intraepithelial neoplasia to micro-invasive carcinoma is characterized by integration of HPV 16/18 and numerical chromosome abnormalities, J. Pathol. 202 (2004) 23–33, https://doi.org/10.1002/path.1490.
[140] L. Cabel, E. Jeannot, I. Bieche, S. Vacher, C. Callens, L. Bazire, A. Morel, A. Bernard-Tessier, W. Chemlali, A. Schnitzler, A. Lievre, J. Otz, M. Minsat, A. Vincent-Salomon, J.Y. Pierga, B. Buecher, P. Mariani, C. Proudhon, F.C. Bidard, W. Cacheux, Prognostic impact of residual HPV ctDNA detection after chemoradiotherapy for anal squamous cell carcinoma, Clin. Cancer Res. (2018), https://doi.org/10.1158/1078-0432.CCR-18-0922 clincanres.0922.2018 [pii]. (1078–0432.CCR-18-0922 [pii]).
[141] L. Cabel, F.C. Bidard, V. Servois, W. Cacheux, P. Mariani, E. Romano, M. Minsat, I. Bieche, F. Farkhondeh, E. Jeannot, B. Buecher, HPV circulating tumor DNA to monitor the efficacy of anti-PD-1 therapy in metastatic squamous cell carcinoma of the anal canal: a case report, Int. J. Cancer 141 (2017) 1667–1670, https://doi.org/10.1002/ijc.30863.
[142] J.Y. Lee, I. Garcia-Murillas, R.J. Cutts, D.G. De Castro, L. Grove, T. Hurley, F. Wang, C. Nutting, K. Newbold, K. Harrington, N. Turner, S. Bhide, Predicting response to radical (chemo)radiotherapy with circulating HPV DNA in locally advanced head and neck squamous carcinoma, Br. J. Cancer 117 (2017) 876–883, https://doi.org/10.1038/bjc.2017.258 (bjc2017258 [pii]).
[143] Y. Song, H. Xiao, Z. Yang, M. Geng, J. Ma, Y. Ren, Y. Liu, G. Wang, The predictive value of pre- and post-induction chemotherapy plasma EBV DNA level and tumor volume for the radiosensitivity of locally advanced nasopharyngeal carcinoma, EXCLI J. 16 (2017) 1268–1275, https://doi.org/10.17179/excli2017-752 (2017-752 [pii] Doc1268 [pii]).
[144] J. Zhang, C. Shu, Y. Song, Q. Li, J. Huang, X. Ma, Epstein-Barr virus DNA level as a novel prognostic factor in nasopharyngeal carcinoma: A meta-analysis, Medicine (Baltimore) 95 (2016) e5130, https://doi.org/10.1097/MD.0000000000005130 (00005792-201610040-00078 [pii]).
[145] H. Peng, L. Chen, Y. Zhang, R. Guo, W.F. Li, Y.P. Mao, L.L. Tan, Y. Sun, F. Zhang, L.Z. Liu, L. Tian, A.H. Lin, J. Ma, Survival analysis of patients with advanced-stage nasopharyngeal carcinoma according to the Epstein-Barr virus status, Oncotarget 7 (2016) 24208–24216, https://doi.org/10.18632/oncotarget.8144.
[146] W.H. Chen, L.Q. Tang, S.S. Guo, Q.Y. Chen, L. Zhang, L.T. Liu, C.N. Qian, X. Guo, D. Xie, M.S. Zeng, H.Q. Mai, Prognostic value of plasma epstein-barr virus DNA for local and regionally advanced nasopharyngeal carcinoma treated with cisplatin-based Concurrent chemoradiotherapy in intensity-modulated radiotherapy era, Medicine (Baltimore) 95 (2016) e2642, , https://doi.org/10.1097/MD.0000000000002642.
[147] J.J. Yao, L. Lin, Y.N. Jin, S.Y. Wang, W.J. Zhang, F. Zhang, G.Q. Zhou, Z.B. Cheng, Z.Y. Qi, Y. Sun, Prognostic value of serum Epstein-Barr virus antibodies in patients with nasopharyngeal carcinoma and undetectable pretreatment Epstein-Barr virus DNA, Cancer Sci. 108 (2017) 1640–1647, https://doi.org/10.1111/cas.13296.
[148] D. Martin, F. Rodel, R. Winkelmann, P. Balermpas, C. Rodel, E. Fokas, Peripheral leukocytosis is Inversely correlated with intratumoral CD8+ T-cell infiltration and associated with worse outcome after chemoradiotherapy in anal cancer, Front. Immunol. 8 (2017) 1225, https://doi.org/10.3389/fimmu.2017.01225.
[149] P. Blanchard, A. Lee, S. Marguet, J. Leclercq, W.T. Ng, J. Ma, A.T. Chan, P.Y. Huang, E. Benhamou, G. Zhu, D.T. Chua, Y. Chen, H.Q. Mai, D.L. Kwong, S.L. Cheah, J. Moon, Y. Tung, K.H. Chi, G. Fountzilas, L. Zhang, E.P. Hui, T.X. Lu, J. Bourhis, J.P. Pignon, Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis, Lancet Oncol. 16 (2015) 645–655, https://doi.org/10.1016/S1470-2045(15)70126-9 (S1470–2045(15)70126–9 [pii]).
[150] J. Lu, M. Murakami, S.C. Verma, Q. Cai, S. Haldar, R. Kaul, M.A. Wasik, J. Middeldorp, E.S. Robertson, Epstein-Barr Virus nuclear antigen 1 (EBNA1) confers resistance to apoptosis in EBV-positive B-lymphoma cells through up-regulation of survivin, Virology 410 (2011) 64–75, https://doi.org/10.1016/j.virol.2010.10.029 (S0042–6822(10)00676–8 [pii]).
[151] L. Sun, Y. Zhao, H. Shi, C. Ma, L. Wei, LMP-1 induces survivin expression to inhibit cell apoptosis through the NF-kappaB and PI3K/Akt signaling pathways in nasal NK/T-cell lymphoma, Oncol. Rep. 33 (2015) 2253–2260, https://doi.org/10.3892/or.2015.3847.
[152] F. Rodel, S. Reichert, T. Sprenger, U.S. Gaipl, J. Mirsch, T. Liersch, S. Fulda, C. Rodel, The role of survivin for radiation oncology: moving beyond apoptosis inhibition, Curr. Med. Chem. 18 (2011) 191–199 (BSP/CMC/E-Pub/2011/012 [pii]).
[153] Y. Zhao, Y. Wang, S. Zeng, X. Hu, LMP1 expression is positively associated with metastasis of nasopharyngeal carcinoma: evidence from a meta-analysis, J. Clin. Pathol. 65 (2012) 41–45, https://doi.org/10.1136/jclinpath-2011-200198 (jclinpath-2011-200198 [pii]).
[154] A. Rahbar, G. Stragliotto, A. Orrego, I. Peredo, C. Taher, J. Willems, C. Soderberg-Naucler, Low levels of Human Cytomegalovirus Infection in Glioblastoma multiforme associates with patient survival; −a case-control study, Herpesviridae 3 (3) (2012), https://doi.org/10.1186/2042-4280-3-3 (2042-4280-3-3 [pii]).
[155] A. Rahbar, A. Orrego, I. Peredo, M. Dzabic, N. Wolmer-Solberg, K. Straat, G. Stragliotto, C. Soderberg-Naucler, Human cytomegalovirus infection levels in glioblastoma multiforme are of prognostic value for survival, J. Clin. Virol. 57 (2013) 36–42, https://doi.org/10.1016/j.jcv.2012.12.018 (S1386–6532(12)00472–6 [pii]).
[156] N. Goerig, S. Semrau, B. Frey, K. Korn, B. Fleckenstein, K. Uberla, A. Dorfler, F. Putz, U.S. Gaipl, R. Fietkau, Clinically significant CMV (re)activation during or after radiotherapy/chemotherapy of the brain: Correlation with neurological deterioration and improvement upon antiviral treatment, Strahlenther. Onkol. 192 (2016) 489–497, https://doi.org/10.1007/s00066-016-0987-7 ([pii]).
[157] K.A. Batich, E.A. Reap, G.E. Archer, L. Sanchez-Perez, S.K. Nair, R.J. Schmittling, P. Norberg, W. Xie, J.E. Herndon 2nd, P. Healy, R.E. McLendon, A.H. Friedman, H.S. Friedman, D. Bigner, G. Vlahovic, D.A. Mitchell, J.H. Sampson, Long-term survival in glioblastoma with cytomegalovirus pp65-targeted vaccination, Clin. Cancer Res. 23 (2017) 1898–1909, https://doi.org/10.1158/1078-0432.CCR-16-2057 (23/8/1898 [pii]).
[158] M.J.P. Welters, W. Ma, S. Santegoets, R. Goedemans, I. Ehsan, E.S. Jordanova, V.J. van Ham, V. van Unen, F. Koning, S.I. van Egmond, P. Charoentong, Z. Trajanoski, L.A. van der Velden, S.H. van der Burg, Intratumoral HPV16-specific T cells constitute a type I-oriented tumor microenvironment to improve survival in HPV16-driven oropharyngeal cancer, Clin. Cancer Res. 24 (2018) 634–647, https://doi.org/10.1158/1078-0432.CCR-17-2140 (1078–0432.CCR-17-2140 [pii]).
[159] S. Demaria, S.C. Formenti, Role of T lymphocytes in tumor response to radiotherapy, Front. Oncol. 2 (2012) 95, https://doi.org/10.3389/fonc.2012.00095.
[160] M.K. Keck, Z. Zuo, A. Khattri, T.P. Stricker, C.D. Brown, M. Imanguli, D. Rieke, K. Endhardt, P. Fang, J. Bragelmann, R. DeBoer, M. El-Dinali, S. Aktolga, Z. Lei, P. Tan, S.G. Rozen, R. Salgia, R.R. Weichselbaum, M.W. Lingen, M.D. Story,

K.K. Ang, E.E. Cohen, K.P. White, E.E. Vokes, T.Y. Seiwert, Integrative analysis of head and neck cancer identifies two biologically distinct HPV and three non-HPV subtypes, Clin. Cancer Res. 21 (2015) 870–881, https://doi.org/10.1158/1078-0432.CCR-14-2481 ([pii]).

[161] C.S. Kong, B. Narasimhan, H. Cao, S. Kwok, J.P. Erickson, A. Koong, N. Pourmand, Q.T. Le, The relationship between human papillomavirus status and other molecular prognostic markers in head and neck squamous cell carcinomas, Int. J. Radiat. Oncol. Biol. Phys. 74 (2009) 553–561, https://doi.org/10.1016/j.ijrobp.2009.02.015 (S0360–3016(09)00247–8 [pii]).

[162] P. Balermpas, F. Rodel, C. Weiss, C. Rodel, E. Fokas, Tumor-infiltrating lymphocytes favor the response to chemoradiotherapy of head and neck cancer, Oncoimmunology 3 (2014) e27403, , https://doi.org/10.4161/onci.27403 (2013ONCOIMM0349 [pii]).

[163] P. Balermpas, Y. Michel, J. Wagenblast, O. Seitz, C. Weiss, F. Rodel, C. Rodel, E. Fokas, Tumour-infiltrating lymphocytes predict response to definitive chemoradiotherapy in head and neck cancer, Br. J. Cancer 110 (2014) 501–509, https://doi.org/10.1038/bjc.2013.640 (bjc2013640 [pii]).

[164] P. Balermpas, F. Rodel, C. Rodel, M. Krause, A. Linge, F. Lohaus, M. Baumann, I. Tinhofer, V. Budach, E. Gkika, M. Stuschke, M. Avlar, A.L. Grosu, A. Abdollahi, J. Debus, C. Bayer, S. Stangl, C. Belka, S. Pigorsch, G. Multhoff, S.E. Combs, D. Monnich, D. Zips, E. Fokas, CD8+ tumour-infiltrating lymphocytes in relation to HPV status and clinical outcome in patients with head and neck cancer after postoperative chemoradiotherapy: A multicentre study of the German cancer consortium radiation oncology group (DKTK-ROG), Int. J. Cancer 138 (2016) 171–181, https://doi.org/10.1002/ijc.29683.

[165] M.J. Gooden, G.H. de Bock, N. Leffers, T. Daemen, H.W. Nijman, The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis, Br. J. Cancer 105 (2011) 93–103, https://doi.org/10.1038/bjc.2011.189.

[166] V. Sridharan, D.N. Margalit, S.A. Lynch, M. Severgnini, J. Zhou, N.G. Chau, G. Rabinowits, J.H. Lorch, P.S. Hammerman, F.S. Hodi, R.I. Haddad, R.B. Tishler, J.D. Schoenfeld, Definitive chemoradiation alters the immunologic landscape and immune checkpoints in head and neck cancer, Br. J. Cancer 115 (2016) 252–260, https://doi.org/10.1038/bjc.2016.166.

[167] X. Chen, B. Yan, H. Lou, Z. Shen, F. Tong, A. Zhai, L. Wei, F. Zhang, Immunological network analysis in HPV associated head and neck squamous cancer and implications for disease prognosis, Mol. Immunol. 96 (2018) 28–36 S0161–5890(18)30029–4 [pii] https://doi.org/10.1016/j.molimm.2018.02.005.

[168] B. Solomon, R.J. Young, D. Rischin, Head and neck squamous cell carcinoma: Genomics and emerging biomarkers for immunomodulatory cancer treatments, Semin. Cancer Biol. (2018), https://doi.org/10.1016/j.semcancer.2018.01.008 S1044-579X(17)30256–0 [pii].

[169] C. Badoual, S. Hans, N. Merillon, C. Van Ryswick, P. Ravel, N. Benhamouda, E. Levionnois, M. Nizard, A. Si-Mohamed, N. Besnier, A. Gey, R. Rotem-Yehudar, H. Pere, T. Tran, C.L. Guerin, A. Chauvat, E. Dransart, C. Alanio, S. Albert, B. Barry, F. Sandoval, F. Quintin-Colonna, P. Bruneval, W.H. Fridman, F.M. Lemoine, S. Oudard, L. Johannes, D. Olive, D. Brasnu, E. Tartour, PD-1-expressing tumor-infiltrating T cells are a favorable prognostic biomarker in HPV-associated head and neck cancer, Cancer Res. 73 (2013) 128–138, https://doi.org/10.1158/0008-5472.CAN-12-2606 (0008–5472.CAN-12-2606 [pii]).

[170] P. Balermpas, F. Rodel, M. Krause, A. Linge, F. Lohaus, M. Baumann, I. Tinhofer, V. Budach, A. Sak, M. Stuschke, E. Gkika, A.L. Grosu, A. Abdollahi, J. Debus, S. Stangl, U. Ganswindt, C. Belka, S. Pigorsch, G. Multhoff, S.E. Combs, S. Welz, D. Zips, S.Y. Lim, C. Rodel, E. Fokas, The PD-1/PD-L1 axis and human Papilloma virus in patients with head and neck cancer after adjuvant chemoradiotherapy: A multicentre study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG), Int. J. Cancer 141 (2017) 594–603, https://doi.org/10.1002/ijc.30770.

[171] R.L. Ferris, G. Blumenschein Jr., J. Fayette, J. Guigay, A.D. Colevas, L. Licitra, K. Harrington, S. Kasper, E.E. Vokes, C. Even, F. Worden, N.F. Saba, L.C. Iglesias Docampo, R. Haddad, T. Rordorf, N. Kiyota, M. Tahara, M. Monga, M. Lynch, W.J. Geese, J. Kopit, J.W. Shaw, M.L. Gillison, Nivolumab for recurrent squamous-cell carcinoma of the head and neck, N. Engl. J. Med. 375 (2016) 1856–1867, https://doi.org/10.1056/NEJMoa1602252.

[172] T.Y. Seiwert, B. Burtness, R. Mehra, J. Weiss, R. Berger, J.P. Eder, K. Heath, T. McClanahan, J. Lunceford, C. Gause, J.D. Cheng, L.Q. Chow, Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial, Lancet Oncol. 17 (2016) 956–965, https://doi.org/10.1016/S1470-2045(16)30066-3.

[173] D. Martin, F. Rodel, P. Balermpas, C. Rodel, E. Fokas, The immune microenvironment and HPV in anal cancer: Rationale to complement chemoradiation with immunotherapy, Biochim. Biophys. Acta 1868 (2017) 221–230 S0304-419X(17)30058–6 [pii] https://doi.org/10.1016/j.bbcan.2017.05.001.

[174] D.C. Gilbert, E. Serup-Hansen, D. Linnemann, E. Hogdall, C. Bailey, J. Summers, H. Havsteen, G.J. Thomas, Tumour-infiltrating lymphocyte scores effectively stratify outcomes over and above p16 post chemo-radiotherapy in anal cancer, Br. J. Cancer 114 (2016) 134–137, https://doi.org/10.1038/bjc.2015.448 (bjc2015448 [pii]).

[175] P. Balermpas, D. Martin, U. Wieland, M. Rave-Frank, K. Strebhardt, C. Rodel, E. Fokas, F. Rodel, Human Papilloma virus load and PD-1/PD-L1, CD8(+) and FOXP3 in anal cancer patients treated with chemoradiotherapy: Rationale for immunotherapy, Oncoimmunology 6 (2017) e1288331, , https://doi.org/10.1080/2162402X.2017.1288331 (1288331 [pii]).

[176] W.H. Hu, K. Miyai, L.C. Cajas-Monson, L. Luo, L. Liu, S.L. Ramamoorthy, Tumor-infiltrating CD8(+) T lymphocytes associated with clinical outcome in anal squamous cell carcinoma, J. Surg. Oncol. 112 (2015) 421–426, https://doi.org/10.1002/jso.23998.

[177] Y.J. Zhao, W.P. Sun, J.H. Peng, Y.X. Deng, Y.J. Fang, J. Huang, H.Z. Zhang, D.S. Wan, J.Z. Lin, Z.Z. Pan, Programmed death-ligand 1 expression correlates with diminished CD8+ T cell infiltration and predicts poor prognosis in anal squamous cell carcinoma patients, Cancer Manag. Res. 10 (2018) 1–11, https://doi.org/10.2147/CMAR.S153965.

[178] R. Govindarajan, S. Gujja, E.R. Siegel, A. Batra, A. Saeed, K. Lai, J.D. James, B.J. Fogel, S. Williamson, Programmed cell death-ligand 1 (PD-L1) expression in anal cancer, Am. J. Clin. Oncol. (2016), https://doi.org/10.1097/COC.0000000000000343.

[179] M.L. Ooft, J.A. van Ipenburg, W.W. Braunius, C.I. Zuur, S. Koljenovic, S.M. Willems, Prognostic role of tumor infiltrating lymphocytes in EBV positive and EBV negative nasopharyngeal carcinoma, Oral Oncol. 71 (2017) 16–25 S1368–8375(17)30132-X [pii] https://doi.org/10.1016/j.oraloncology.2017.05.015.

[180] M.L. Ooft, J.A. van Ipenburg, M.E. Sanders, M. Kranendonk, I. Hofland, R. de Bree, S. Koljenovic, S.M. Willems, Prognostic role of tumour-associated macrophages and regulatory T cells in EBV-positive and EBV-negative nasopharyngeal carcinoma, J. Clin. Pathol. (2017), https://doi.org/10.1136/jclinpath-2017-204664 jclinpath-2017-204664 [pii].

[181] G. Kroemer, L. Galluzzi, O. Kepp, L. Zitvogel, Immunogenic cell death in cancer therapy, Annu. Rev. Immunol. 31 (2013) 51–72, https://doi.org/10.1146/annurev-immunol-032712-100008.

[182] U.S. Gaipl, G. Multhoff, H. Scheithauer, K. Lauber, S. Hehlgans, B. Frey, F. Rodel, Kill and spread the word: stimulation of antitumor immune responses in the context of radiotherapy, Immunotherapy 6 (2014) 597–610, https://doi.org/10.2217/imt.14.38.

[183] A.B. Sharabi, M. Lim, T.L. DeWeese, C.G. Drake, Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy, Lancet Oncol. 16 (2015) e498–e509, https://doi.org/10.1016/S1470-2045(15)00007-8 (S1470–2045(15)00007–8 [pii]).

[184] S. Demaria, E.B. Golden, S.C. Formenti, Role of local radiation therapy in cancer immunotherapy, JAMA Oncol. 1 (2015) 1325–1332, https://doi.org/10.1001/jamaoncol.2015.2756 (2425837 [pii]).

[185] A. Levy, G. Nigro, P.J. Sansonetti, E. Deutsch, Candidate immune biomarkers for radioimmunotherapy, Biochim. Biophys. Acta 1868 (2017) 58–68 S0304-419X(17)30008–2 [pii] https://doi.org/10.1016/j.bbcan.2017.02.006.

[186] M.W. Teng, S.F. Ngiow, A. Ribas, M.J. Smyth, Classifying cancers based on T-cell infiltration and PD-L1, Cancer Res. 75 (2015) 2139–2145, https://doi.org/10.1158/0008-5472.CAN-15-0255.

[187] J.M. Taube, R.A. Anders, G.D. Young, H. Xu, R. Sharma, T.L. McMiller, S. Chen, A.P. Klein, D.M. Pardoll, S.L. Topalian, L. Chen, Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape, Sci. Transl. Med. 4 (2012) 127ra137, https://doi.org/10.1126/scitranslmed.3003689.

[188] C.Y. Ock, B. Keam, S. Kim, J.S. Lee, M. Kim, T.M. Kim, Y.K. Jeon, D.W. Kim, D.H. Chung, D.S. Heo, Pan-cancer immunogenomic perspective on the tumor microenvironment based on PD-L1 and CD8 T-cell infiltration, Clin. Cancer Res. 22 (2016) 2261–2270, https://doi.org/10.1158/1078-0432.CCR-15-2834 (1078–0432.CCR-15-2834 [pii]).

[189] H. Safran, K.L. Leonard, K. Perez, M. Vrees, A. Klipfel, S. Schechter, N. Oldenburg, L. Roth, N. Shah, K. Rosati, L. Rajdev, K. Mantripragada, I.Y. Sheng, P. Barth, T.A. DiPetrillo, Tolerability of ADXS11–001 Lm-LLO listeria-based immunotherapy with mitomycin, fluorouracil, and radiation for anal cancer, Int. J. Radiat. Oncol. Biol. Phys. 100 (2018) 1175–1178 S0360–3016(18)30004-X [pii] https://doi.org/10.1016/j.ijrobp.2018.01.004.

[190] E.A. Chiocca, S.D. Rabkin, Oncolytic viruses and their application to cancer immunotherapy, Cancer Immunol. Res. 2 (2014) 295–300, https://doi.org/10.1158/2326-6066.CIR-14-0015 (2/4/295 [pii]).

[191] N. Woller, E. Gurlevik, B. Fleischmann-Mundt, A. Schumacher, S. Knocke, A.M. Kloos, M. Saborowski, R. Geffers, M.P. Manns, T.C. Wirth, S. Kubicka, F. Kuhnel, Viral infection of tumors overcomes resistance to PD-1-immunotherapy by broadening neoantigenome-directed T-cell responses, Mol. Ther. 23 (2015) 1630–1640, https://doi.org/10.1038/mt.2015.115.

[192] B. Frey, M. Ruckert, L. Deloch, P.F. Ruhle, A. Derer, R. Fietkau, U.S. Gaipl, Immunomodulation by ionizing radiation-impact for design of radio-immunotherapies and for treatment of inflammatory diseases, Immunol. Rev. 280 (2017) 231–248, https://doi.org/10.1111/imr.12572.