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Oncolytic bovine herpesvirus type 1 as a broad spectrum cancer therapeutic

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Oncolytic viruses selectively replicate in tumor cells and elicit antitumor effects *in vivo* by both direct and indirect methods. They are attractive avenues of cancer therapy due to the absence of toxic side effects often seen in current treatment modalities. Bovine herpesvirus type 1 (BHV-1) holds promise as a broad-spectrum oncolytic vector that is able to infect and kill human tumor cells from a variety of histological origins, including cancer-initiating cells. In the majority of cases, BHV-1 elicits tumor cell death in the absence of a productive infection. *In vivo*, BHV-1 affects the incidence of secondary lesions in cotton rats bearing subcutaneous breast adenocarcinomas. These recent studies contribute to the characterization of BHV-1 as an oncolytic virus.

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Introduction

BHV-1 biology

Bovine herpesvirus type 1 (BHV-1) is a member of the *Herpesviridae* family that initiates bovine respiratory disease complex in cattle by suppressing the immune system [1,2]. This complex manifests in a wide variety of symptoms resembling the common cold [3,4]. In the absence of a secondary bacterial infection, active BHV-1 infection is cleared by the immune response within 1–2 weeks [3]. BHV-1 is a neurotropic virus that establishes life-long latency in neurons, with reactivation resulting from parturition, pregnancy, transport, concomitant infections, poor living conditions and increases in corticosteroids [3,5].

BHV-1 cellular receptors include heparin sulphate proteoglycans, nectin-1 and the poliovirus receptor CD155, which is commonly upregulated in human cancers and is associated with tumor cell migration and invasion [6,7]. The replication of BHV-1 is tightly regulated, occurring in a sequential manor from immediate early (IE), early and finally late gene expression [5]. During productive infection BHV-1 infected cell protein 0 (bICP0) stimulates viral gene expression, interacts with cellular proteins to promote virus replication and is heavily involved in counteracting the host anti-viral immune response [8–11].

Oncolytic viruses

Oncolytic viruses (OV) selectively replicate in and kill tumor cells while sparing normal cells. This characteristic is either natural (wild type OV) or gained through genetic engineering. The tumor-targeting specific nature of OVs makes them appealing as a cancer therapy due to the lack of off-target toxicities often seen with conventional therapies. Furthermore, their ability to target and kill drug-resistant cells, such as cancer initiating cells (CICs), may allow for sustained patient responses to therapy [12••,13,14]. Data from clinical trials demonstrate the safety and efficacy of OVs and their ability to induce antitumor activity (as reviewed in [15•]). Although human viruses have shown efficacy in clinical trials (as reviewed in [16]), pre-existing immunity presents a barrier to systemic delivery and the treatment of metastatic disease (Figure 1a). This barrier warrants the development of wild type, non-human viruses for oncolytic virotherapy (OVT).

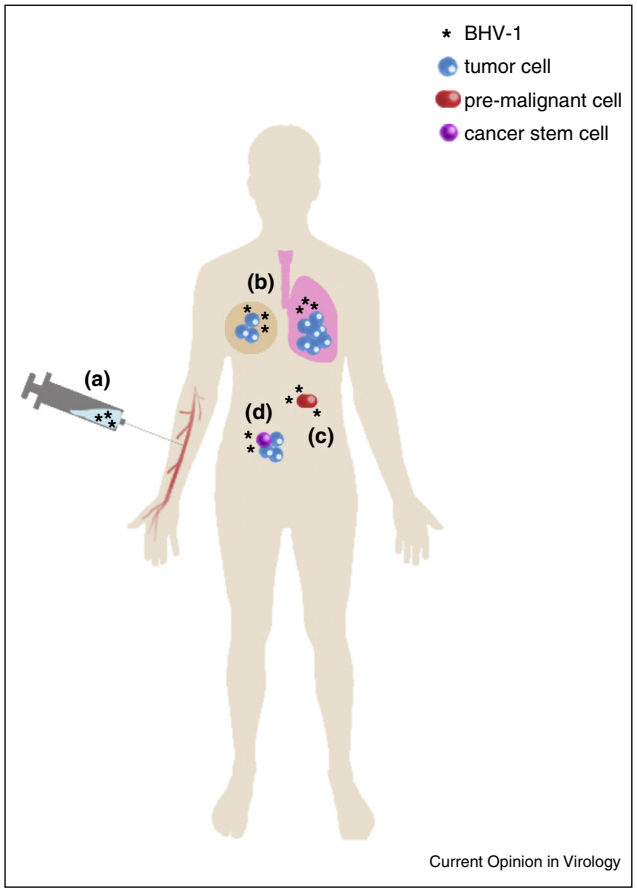
In this article, we review the characterization of BHV-1 as an OV, highlighting its unique and clinically relevant features.

BHV-1 as a broad-spectrum oncolytic virus

High-throughput screening techniques are often used to rapidly evaluate the ability of OVs to infect and kill tumor cells *in vitro*. These assays not only identify tumor types most efficiently killed by the virus but they also allow for the interrogation of pathways that dictate cellular susceptibility. The molecular diversity between and within cancer types warrants the development of novel OVs with distinct mechanisms of tumor cell targeting.

The replication and cytotoxicity of BHV-1 are restricted in normal human cells; however, both human immortalized and transformed cells are sensitive to BHV-1 infection (Figure 1b,c) [17]. A screen for virus replication and cytotoxicity in the NCI60 panel of human tumor cell lines was used to evaluate the oncolytic ability of BHV-1 *in vitro*. Overall, 72% of the panel was permissive to BHV-1

Figure 1



Characteristics of BHV-1 as an oncolytic virus. Unlike human OVs, pre-existing immunity may not present a barrier to the systemic delivery of BHV-1 facilitating the treatment of metastatic disease (**a**). Both human immortalized and transformed cells are sensitive to BHV-1 infection (**b, c**). This allows for the targeting of multiple tumor types and the potential to inhibit growth of pre-malignant lesions. In addition to bulk BC cells, BHV-1 is able to infect and kill BCICs which are thought to contribute to tumor relapse and metastasis (**d**).

infection with corresponding decreases in cellular viability [18••]. Surprisingly, decreases in cellular viability occurred at low multiplicity of infection and were detected in semi-permissive and non-permissive tumor cell lines [18••].

Current breast cancer (BC) treatments are designed and prescribed based on the tumor's molecular profile, including tumor subtype and receptor status. However, multidrug resistance and subsequent patient relapse remains a formidable problem, warranting the development of broadly applicable treatment strategies. The ability of BHV-1 to infect and kill BC cells from a variety of subtypes and with varied receptor expression profiles was tested [12••]. Results showed that BHV-1 is able to infect and kill human BC cells from a variety of subtypes (Figure 2a) [12••]. Similar to the NCI panel screen data, decreases in cellular viability occurred in the absence of a viral burst [12••].

Recent studies have implicated breast cancer initiating cells (BCICs) as major contributors to BC relapse and metastasis. BCIC possess multiple characteristics that confer resistance to conventional therapeutics such as their ability to self-renew, differentiate to give rise to multiple cell lineages and resist apoptosis [19,20]. In addition to bulk BC cells, BHV-1 is able to infect and kill BCICs (Figure 1d) from both luminal and basal subtypes and decrease their ability to self-renew and differentiate [12••]. Furthermore, BCICs have been described as having enhanced tumor forming ability *in vivo*, with as few as 10^3 $CD44^+CD24^{-/low}$ BCICs capable of initiating tumor growth in immunocompromised mice [21,22]. The luminal BC cell line MCF7 contains BCICs which comprise between 0.2 and 7.5% of the total cell population. The infection of bulk MCF7 cells with BHV-1 significantly decreases their ability to form tumors when implanted into immunocompromised mice [12••]. However, tumor formation was not completely abrogated, indicating that while BHV-1 is able to induce cytotoxicity in bulk MCF7 cells it is not able to fully inhibit the tumor forming ability of BCICs *in vivo* [12••].

Results from these studies indicate that BHV-1 has tropism for multiple tumor types, including BC cells and BCICs from multiple subtypes (Figure 2a) [12••,18••]. Consistently, BHV-1-mediated cellular cytotoxicity occurred independent of high levels of virus replication [12••,18••]. While this could limit effective targeting and clearance of tumors *in vivo*, it seems unlikely due to recent studies highlighting the importance of indirect mechanisms of tumor cell destruction, such as antitumor immune responses [23,24,25••]. Furthermore, although a soluble cytotoxic by-product of infection could be responsible for eliciting tumor cell death, this outcome was not observed [12••]. Although the mechanism by which BHV-1 causes tumor cell death remains unknown, it is the focus of future studies.

KRAS and cellular sensitivity to BHV-1

The Rat sarcoma (Ras) superfamily, which includes Kirsten (K)RAS, contains plasma membrane associated proteins that have roles in the control of multiple cellular processes [26]. Mutations in KRAS are associated with lung, colon and prostate tumor types and have been shown to play a role in tumor progression and treatment efficacy [27–29]. Specifically, current lung cancer treatments often have poor efficacy, especially on tumors expressing a KRAS mutation [30,31].

In contrast to other species-specific wild type OVs, defects in type I interferon signaling do not dictate cellular sensitivity to BHV-1 [17,32–34]. A rudimentary screen using the Sanger Institute COSMIC online

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