



IMPACT OF INTRACELLULAR p53 IN DNA VIRAL REPLICATION

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ABSTRACT

The central nervous system (CNS) can be infected by viruses that can cause neuroinflammation. The main DNA viruses capable of infecting the CNS are herpesviruses and some polyomaviruses, which can cause viral encephalitis. The John Cunningham virus (JCV) resides asymptotically in the CNS, but can cause progressive multifocal leukoencephalopathy (PML), with immunodeficiency, permanent neurological deficits, and can possible fatality. Polyomaviruses are double-stranded DNA (dsDNA) viruses, and their replication depends on host cell enzymes. Viral DNA enters the nucleus and hijacks cellular DNA polymerase and cellular transcription factors. PD-1 inhibitors may be effective in restoring the activity of antiviral T cells. The p53 protein is one of the main regulators of the cellular response to stress. p53 is an important tumor suppressor and directly influences viral replication. In the CNS, p53 is activated during stress in response to DNA damage or viral infections and inhibits viral replication and causes cell cycle arrest in the G1/S phase. If this phase is blocked, the virus cannot replicate, and infected cells undergo apoptosis. In conclusion, p53 acts as a transcription factor and induces the expression of pro-apoptotic proteins belonging to the BCL-2 family, such as Bcl-2 Associated X protein (BAX), NOXA, and P53 Upregulated Modulator of Apoptosis (PUMA), which increase mitochondrial membrane permeability, the release of cytochrome C, and activate apoptotic caspases.

KEYWORDS: *Virus, infection, CNS, p53, viral replication*

INTRODUCTION

Viral infections can affect both the brain and the spinal cord of the central nervous system (CNS) (1). Viruses can cause inflammation of the meninges (meningitis), inflammation of the brain (encephalitis), and inflammation of the spinal cord (myelitis) (2). The viruses most frequently involved are arboviruses (which can cause dengue and West Nile disease), herpes simplex, varicella-zoster, and enteroviruses (3). The primary DNA viruses capable of infecting the CNS are mainly herpesviruses and certain polyomaviruses. Polyomaviruses can cause DNA viral encephalitis and progressive multifocal leukoencephalopathy (PML), while more rarely, adenoviruses can cause meningitis or encephalitis, particularly in children and immunocompromised individuals (4).

A diagnosis of infection is established by collecting cerebrospinal fluid via lumbar puncture and analysing it for viral infection using polymerase chain reaction (PCR); other diagnostic tools include magnetic resonance imaging (MRI), and,

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more rarely, electroencephalogram (EEG). Symptoms of infection may include severe headache, often accompanied by confusion, fever, altered mental status, drowsiness, weakness, paralysis, and neck stiffness (5). Treatment depends on the specific type of virus involved; however, it typically consists of hydration, administration of specific antiviral medications, and intensive care if necessary. Encephalitis can be a very serious condition and may result in permanent neurological damage.

The John Cunningham virus (JCV) interacts with the p53 tumor suppressor protein to drive viral replication and potentially promote cellular transformation. JCV are highly significant polyomaviruses capable of causing progressive multifocal leukoencephalopathy (PML) (4). JCV is a very common virus belonging to the polyomavirus family that usually infects people during childhood or adolescence. Infected individuals may not develop symptoms and are often unaware of their infection.

The most important polyomavirus within the CNS is, above all, JCV, which is the causative agent of PML. This virus typically resides in the CNS asymptotically but may become reactivated if the host organism enters a state of immunodeficiency (6). PML primarily targets cerebral myelin and can manifest with cognitive changes, weakness, loss of coordination, seizures, and visual impairments. Treatment for this infection focuses primarily on restoring the immune system (7). The prognosis may be fatal in cases of severe immunodeficiency, or it may result in permanent neurological deficits. Reactivation of the immune system can trigger a severe inflammatory response, which may be managed through the administration of corticosteroids, immunosuppressants, and anti-inflammatory agents (8). Furthermore, anti-inflammatory cytokines, such as the IL-1 receptor antagonist (IL-1RA), may prove beneficial (9).

POLYOMAVIRUSES

Polyomaviruses are double-stranded DNA (dsDNA) viruses; they are non-enveloped and possess a circular dsDNA genome and an icosahedral capsid (10). Polyomavirus replication relies heavily on host cell enzymes and can be targeted at various stages, such as receptor binding or fusion, entry into the host cell, prevention of viral genome release, inhibition of DNA polymerase or viral enzymes, transcription and translation, blockade of viral protein synthesis, prevention of capsid formation, blocking the egress of viral particles, and release (11). Polyomaviruses utilize numerous cellular enzymes and do not possess their own specific DNA polymerase. The viral DNA enters the nucleus and hijacks the cellular DNA polymerase and cellular transcription factors. From a therapeutic standpoint, restoring the immune system proves to be the most effective strategy (12). Furthermore, the use of antiviral drugs can reduce DNA replication; similarly, the use of experimental immunomodulators, such as PD-1 inhibitors, may be effective in restoring the activity of antiviral T cells (13). These therapies aim to interrupt viral replication and enable the immune system to eliminate infected cells.

p53

The *TP53* gene encodes p53 protein and is one of the primary regulators of the cellular stress response (14). p53 regulates the genome, is one of the most important tumor suppressors, and directly affects viral replication. p53 is activated in response to stressors, such as DNA damage or viral infection, and blocks viral replication by inducing cell cycle arrest, primarily at the G1/S transition, and by activating p21 genes (15). These effects are significant because many DNA viruses replicate their genomes specifically during the S phase. If this phase is blocked, the virus cannot replicate, and the infected cells undergo apoptosis.

The p53 protein can activate the mitochondrial apoptotic pathway when a cell is subjected to stress, for instance, from chemical agents or viral infections (resulting in damage to genetic information) (16). p53 acts as a transcription factor, inducing the expression of pro-apoptotic proteins belonging to the BCL-2 family, such as Bcl-2 Associated X protein (BAX), NOXA, and P53 Upregulated Modulator of Apoptosis (PUMA) (16). This causes genetic mutations and induces alterations within the nucleotide sequence and/or the double-helix structure of DNA. p53 increases the permeability of the outer mitochondrial membrane, triggering the release of cytochrome C and the subsequent activation of apoptotic caspases (17). The elimination of the infected cell happens before the virus can complete its replication. p53 can interfere directly with viral proteins, or it can act upon the regulation of viral DNA, the repression of viral transcription, or the interference with viral replication itself (18).

Conversely, viruses have developed new strategies aimed at counteracting and inactivating p53. For example, the adenovirus possesses a protein called E1B that binds to and inactivates p53; the papillomavirus utilizes the E6 protein to degrade p53, while the herpesvirus directly modulates p53 (19). It can be concluded that p53 acts as a critical antagonist to viral replication, as it restricts the S phase, induces premature cell death, interferes with viral transcription and

replication, and compels viruses to develop evasion mechanisms. In summary, p53 upregulates PUMA, NOXA, and BAX, which promote mitochondrial permeabilization, thereby inducing the caspases that mediate apoptosis (20).

PUMA, NOXA, and BAX are pro-apoptotic proteins belonging to the BCL-2 protein family, which governs cell survival or death at the mitochondrial level. BAX is an apoptosis "effector"; when activated together with BAK, it induces pore formation in the mitochondria, leading to increased permeability and the release of cytochrome C, which triggers caspase activation and apoptosis. PUMA is a BH3-only protein capable of neutralizing anti-apoptotic proteins such as BCL-2 and BCL-XL, thereby releasing and/or activating BAX and BAK, and amplifying the apoptotic signal. PUMA is one of the most important transcriptional targets of p53. NOXA is also a BH3-only protein that acts primarily by neutralizing anti-apoptotic proteins, such as MCL-1, and indirectly facilitating the activation of BAX/BAK (21). NOXA is involved in cellular stress responses and viral infections. Thus, PUMA and NOXA remove the anti-apoptotic "brakes," while BAX executes the mitochondrial damage, leading to the activation of the caspase cascade.

When a cell becomes infected by a virus, this mechanism can help eliminate the cell before the pathogen completes its replication, serving as a defensive strategy for the organism's immune system. Some viruses, however, deploy a defensive strategy aimed at inactivating p53.

Following cellular stress, viral infection, or DNA damage, p53 can be downregulated, inducing the expression of PUMA and NOXA, which neutralize anti-apoptotic proteins (Bcl-2, MCL-1), and BAX (and BAK) are activated and oligomerized. The sequence continues with:

- a) Permeabilization of the outer mitochondrial membrane
- b) Release of cytochrome C
- c) Activation of the caspase cascade
- d) Apoptosis of the infected cell

This pathway is important because p53 helps eliminate infected or damaged cells, limiting viral replication and spread.

CONCLUSIONS

In conclusion, viral infections of the CNS pose a serious threat to health, as they can cause neuroinflammation, encephalitis, and permanent damage. Among the main agents involved are herpesviruses and JCV, whose replication depends on host cellular mechanisms. In this context, the p53 protein plays a key role in antiviral defense, as it limits viral replication by arresting the cell cycle and inducing apoptosis of infected cells. Understanding the molecular mechanisms that regulate the interaction between viruses and nerve cells is essential to develop more effective therapeutic strategies.

Conflict of interest

The authors declare that they have no conflict of interest.

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