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REVIEW ARTICLE

MCPyV and Oxidative Stress: Focus on Mechanism of Action Associated with Merkel Cell Carcinoma

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ABSTRACT

Merkel cell carcinoma (MCC) is a life-threatening, aggressive cancer. MCV genome integration into epidermal keratinocytes or dermal fibroblasts leads to polyomavirus-associated MCC (MCCP). Many cancer types show an increased amount of reactive oxygen species (ROS) in the growing and metastatic phases. An increase in the oxidative stress pathway results in an elevated amount of ROS. It is supposed that MCV uses the same mechanisms for inducing cancer. It can be considered that viral MCCs could be the result of oxidative stress pathways in the MCC-causing viral agent, the Merkel cell polyomavirus (MCPyV). The objective of this study was to examine the role of oxidative stress in cancers associated with Merkel cell polyomavirus (MCV). The search strategy was performed in PubMed, NCBI, Google Scholar, EMBASE, and Medline on cancer, oxidative stress, and gene manipulation up to 10 June 2022 by searching the following keywords: MCV, oxidative stress, cancer, and MCC. The cells' uncontrolled increase in ROS amounts results in difficulties including changes in genome structure and instability. Some of these changes account for unwanted replication and inflammation in damaged cells. This investigation of the oxidative stress pathway and its role in MCC highlights new approaches for cancer therapy methods. These free radicals have been proposed to significantly contribute to DNA damage, and reactive oxygen species (ROS) are considered key mediators in the development of Merkel cell carcinoma.

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Introduction

Cancer is one of the controversial diseases these days that is known for its high morbidity and mortality and The number of new cases has dramatically risen by 8.4 million from 2002 to 2020 and 10.0 million deaths worldwide [1,2]. Breast, lung, and prostate cancers represent the most frequently diagnosed malignancies worldwide [2]. A critical point is that cancer is associated with various factors that should be taken into consideration. Therapies vary and they are administered in so many different means. Risk factors for cancer are extremely different from type to type. Consequently, the identification of these causes has encountered many drawbacks. It is known that there is a correlation of a bit over 15-20% between many viruses, bacteria and parasites with cancers [3] There is evidence for the possibility of Human papilloma virus (HPV) leading to many types of cancers, such as cervical, vulva, vagina, penis and anal [4] Much more about Hepatitis B virus (HBV) and its association with hepatocellular carcinoma and the role of hepatitis C virus (HCV) in liver cancer have been proven [5]. One of the most important viruses that we are about to take under consideration is Merkel Cell Virus (MCV). This virus comes from the Polyomaviridae family, which has small double-stranded DNA without an envelope and can be derived from humans. Interaction between large T-antigen of MCV with p53 and PKB(Protein-kinase B) can lead to uncontrolled cell proliferation [6]. Later, the relationship between MCV and Merkel Cell Carcinoma was found by Toker in 1972 then Trabecular carcinoma renamed to Merkel cell carcinoma, polyomavirus was discovered in 2008 [7-9]. Merkel cell carcinoma (MCC) is a malignant neuroendocrine carcinoma of the skin. The rate of new cases is increasing rapidly and it may be difficult to diagnose, at the primary stages. It is more common in people over 70 years compared to other age groups. UV radiation and reactive oxygen species (ROS) play a striking role in the development of MCC [10] (Figures 1 and 2). As we know, free radicals can be produced by mitochondria in human cells or with detrimental products. [11] Chronic oxidative stress (OS) induced by viruses and environmental factors can be conducive to critical DNA damage [12]. Studies have illustrated that free radicals, including reactive oxygen species (ROS) are involved in the process of carcinogenesis [13]. But the immune system is not alone in this unfair battle. The antioxidant system, which includes various types of antioxidants, contributes significantly to decreasing ROS levels in cells. Therefore, there is a strong relationship between the amounts of antioxidants in the body and cancers. When the equilibrium between reactive oxygen species generation and cellular antioxidant defenses is disrupted, oxidative stress develops, leading to damage of DNA and other essential biomolecules [14]. Our study aimed to investigate the relationship between cancer and oxidative stress, by focusing on Viral human MCC and the role of MCPyV in it. The search strategy performed in Google Scholar, PubMed, NCBI, EMBASE, Medline, Scopus, and Nature up to 2022 with no language nor other specific restrictions by searching the following keywords: Cancer, Cancer types, immune responses, Oxidative stress, Merkel cell, Merkel cell carcinoma(MCC), skin cancer, reactive oxygen species (ROS), Merkel cell polyomavirus (MCV), free radicals, polyomavirus-associated MCC (MCCP), non-viral MCC (MCCN), oxidative stress and Merkel cell, oxidative stress effects on MCC, programmed death 1 (PD1), programmed death 1 ligand (PDL1). We removed duplicated articles with the same content. Screening just the title abstract removed articles with the incoherent subject and the review articles. The remaining articles were assessed precisely for content competency.

Findings

Merkel cell polyomavirus (MCPyV) is a small, non-enveloped virus with a double-stranded DNA genome that has been strongly implicated in the development of Merkel cell carcinoma (MCC), a rare yet highly aggressive cutaneous malignancy [15,16]. MCC was initially characterized in 1972 by Cyril Toker and has since been recognized as a rapidly progressive skin cancer with a strong association with states of immunosuppression [17]. Although compromised immune function represents the primary predisposing factor for MCC, environmental contributors—particularly ultraviolet (UV) radiation—also play a significant role in disease development. However, the precise UV action spectrum, exposure pattern, and threshold dose required to induce carcinogenic effects in MCC remain insufficiently defined [18]. MCPyV infection is prevalent and often asymptomatic in the general population [26,27]. In cases of prolonged persistent infection, the virus replicates and remains in an episomal form within infected, non-malignant human cells. The viral DNA found in Merkel cell carcinomas (MCCs) is often integrated into the host genome. Integration typically occurs at random locations within the genome, though chromosome 5 is a frequent site [28-30]. The virus can integrate as either a single copy or as a concatemer composed of multiple copies [28]. This integration event usually leads to tumor-specific truncation mutations, which allow for the continued expression of sT and LT truncation (LTT) mutants that preserve the N-terminal RB-binding LXCXE motif. This motif is crucial for inhibiting the tumor-suppressor function of RB (Figure 1B) [22,31-34]. The LTT and sT proteins, expressed from the integrated viral genome, are the primary oncoproteins driving the growth and

survival of tumor cells [33-37]. Since MCPyV was first identified over ten years ago, research has mainly focused on how the virus-encoded oncoproteins contribute to cellular transformation and MCC development. Numerous reviews have summarized these findings [38, 42]. However, the complete life cycle of MCPyV and its role in MCC development remain poorly understood. Further research in this area is crucial for developing more effective treatments for MCC [19,21,43]. This review aims to address the gaps in our understanding of the biological mechanisms behind MCPyV-associated oncogenesis. Initially, Merkel cell carcinoma (MCC) was thought to originate from Merkel cells, a rare subset of mechanoreceptor cells in the skin's epidermis [20,44]. However, following the discovery of MCPyV in 2008 [22], evidence soon emerged indicating that MCPyV causes asymptomatic and persistent

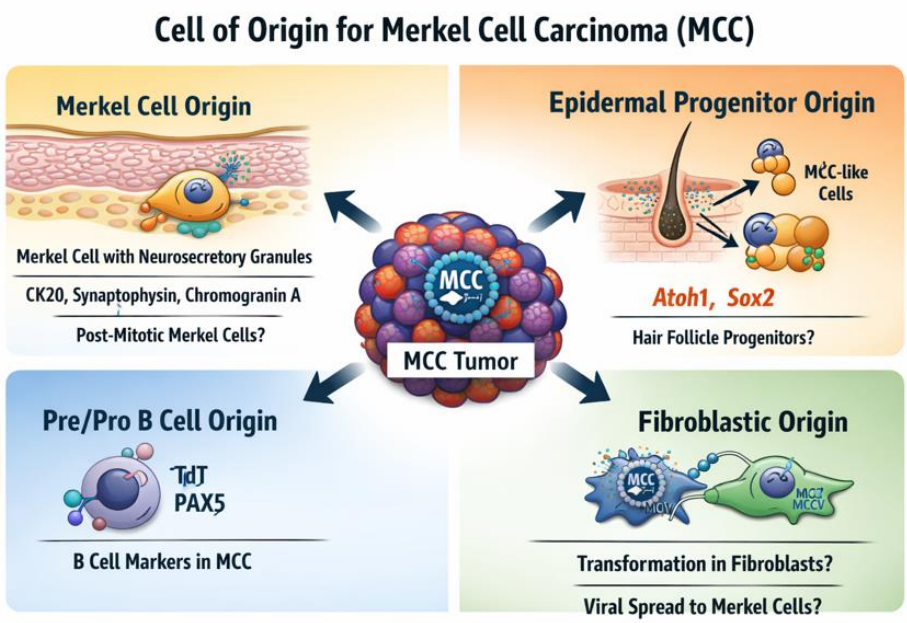

Fig. 1. This infographic illustrates the various proposed origins of Merkel Cell Carcinoma (MCC), including Merkel cells, epidermal progenitor cells, pre/pro B cells, and fibroblasts. Key references include studies on Merkel cell markers (CK20, synaptophysin, chromogranin A) [44,72-75], the role of progenitor cells in mixed tumors [76,77], B cell markers in MCC [78], and fibroblasts' involvement in MCPyV infection and MCC development [63,79,80].

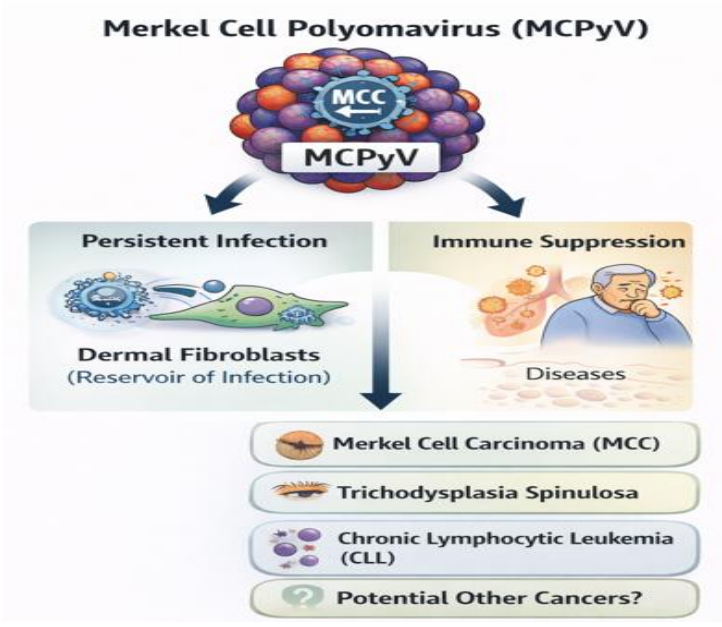

Fig. 2. This infographic illustrates the potential outcomes of Merkel Cell Polyomavirus (MCPyV) infection, including persistent infection in dermal fibroblasts and immune suppression. MCPyV is associated with several diseases, including Merkel Cell Carcinoma (MCC), Trichodysplasia Spinulosa, and Chronic Lymphocytic Leukemia (CLL), with potential links to other cancers. [81,82]

infections in a significant portion of the population [23,26,27,45,48]. Initial exposure typically occurs in early childhood, with seroprevalence increasing with age [26,45,46,49,50]. As expected, given its association with MCC, MCPyV is primarily detected in the skin [26, 51], though it has also been found in other bodily fluids, including respiratory samples, urine, and blood [52, 57]. Schowalter et al. (2010) demonstrated that MCPyV is constantly shed from the skin, with millions of viral genomes detectable in skin swabs [26]. They proposed that because the relatively few Merkel cells in the skin may not be sufficient to support such extensive viral production, the primary host cell for MCPyV infection is more likely a common skin cell type, such as keratinocytes or melanocytes. It was also suggested that MCPyV infection is closely linked to epidermal differentiation, similar to the mechanisms of HPV infection in keratinocytes [26]. To pinpoint the specific cell types that serve as the host for MCPyV, several studies investigated the viral entry mechanism. It was found that glycosaminoglycans, particularly heparan sulfate, are crucial for the virus's initial attachment to host cells, and that an unknown co-receptor is necessary for complete viral entry. This mechanism was found to be similar to that used by HPV to enter cells [24]. After the virus enters the cell, trafficking from the endosome to the endoplasmic reticulum appears to be another key step that limits viral infection, adding a further layer to its host tropism [59]. Throughout the 2010s, multiple attempts were made to create a cell culture system for MCPyV infection and identify its infectious host cell. Neumann et al. developed a transfection system where a consensus MCPyV genome could replicate in several cell lines [60]. Similarly, Feng et al. created a replicating MCPyV genome system [61]. In 2011, Schowalter et al. established cell systems capable of supporting MCPyV replication [24]. However, challenges remained in identifying a relevant primary cell type that supports infection by native virions [25]. Aside from the U2OS osteosarcoma cell line, which supports low-level MCPyV infection [62], no other permissive cell type was identified until 2016, when our group discovered that human dermal fibroblasts (HDFs) alone supported the full MCPyV infectious cycle [63]. Interestingly, Merkel cells do not support MCPyV infection, and keratinocytes were only permissive for pseudovirus entry but not for native virus replication or gene expression [63]. Further analysis of ex vivo skin cultures revealed that MCPyV preferentially infects dermal fibroblasts located beneath the epidermal basal layer and around hair follicles [63]. Prior studies had shown that MCPyV virions are commonly detected in eyebrow hair bulbs from healthy individuals [64, 66]. These findings suggest that MCPyV may use the follicular space to spread to the skin surface and infect new hosts [63]. The natural host cells that maintain latent MCPyV infection remain unknown. MCPyV has been detected in various tissues [52,57,67], suggesting that it may also establish reservoirs in locations other than the skin, such as the tonsils or blood, particularly in inflammatory monocytes [56,57,67]. Additionally, host cell factors such as phosphorylation of viral proteins [68] and host immune responses [69,70] may further influence MCPyV infection. Researchers also observed that MCPyV has an extremely narrow tropism. Among fibroblasts from common model animals, only chimpanzee and human fibroblasts support significant MCPyV infection [71]. This limited host range complicates the development of in vivo infection models [71]. As suggested by previous studies, engineering MCPyV chimeras with mammalian polyomaviruses could provide a potential solution to this challenge [71,80].

Effect of Oxidative Stress on carcinogenesis

Chronic inflammatory conditions, particularly those involving interactions between reactive oxygen species (ROS) produced by myeloid cells and tumor necrosis factor-alpha (TNF-α)–dependent signaling pathways, have been implicated in the initiation and progression of carcinogenesis. Prolonged exposure to elevated ROS concentrations is widely recognized as a major cause of DNA damage [83]. Such damage often manifests as genomic instability and the formation of fragile chromosomal regions. Importantly, the loss of one allele of a tumor suppressor gene does not invariably result in complete pathway dysfunction, especially when compensatory mechanisms such as promoter methylation or mutational events are absent in the remaining allele. These observations raise a fundamental question regarding the nature of carcinogenesis: whether tumor development arises from random genetic alterations followed by selective pressure, or from non-random,

Fig. 3. Pax-6 effect on ROS levels results in elevated levels of TGF-B. TGF-B acts as suppressor of Th1 and Th2 function which results in tumor escape from immune system.

targeted genetic changes that undergo selection. Addressing this distinction may significantly influence chemopreventive strategies in specific cancer contexts. Consequently, increasing attention has been directed toward mapping oxidative nucleic acid damage in relation to genomic architecture and cellular organization. Extensive in vitro investigations using purified DNA and cultured cell systems have demonstrated that oxidative damage does not occur uniformly across the genome; rather, certain regions, including telomeric sequences, appear particularly susceptible. However, findings derived from in vitro models require systematic validation at the tissue and organ levels. Advances in whole-genome sequencing across multiple species have now made such analyses increasingly feasible.It is also critical to consider that nuclear DNA is tightly associated with histone proteins and organized into chromatin, where only selected regions remain transcriptionally accessible. Susceptibility to oxidative stress may therefore differ depending on cell type, chromatin state, and environmental context. This heterogeneity may help explain the diversity of signaling pathways activated across different cancer types. While precision cancer therapy continues to evolve, cancer prevention remains equally important, particularly in light of the growing economic burden of oncologic care. The future development of personalized cancer prevention strategies will require the identification of reliable biomarkers of oxidative stress and oxidative stress–associated preneoplastic alterations [84]. In this context, the present review focuses on the roles of Pax6, p62, and G6PD in oxidative stress–mediated mechanisms underlying Merkel cell carcinoma.

Pax6 and oxidative stress

Pax6 belongs to the Pax gene family and produces the Pax-6 transcription factor, which is crucial for cellular development and differentiation (Figure 3). Earlier research has shown that oxidative stress can influence the subcellular localization of Pax6, causing it to accumulate in the cytoplasm of adult corneal epithelial cells. To determine whether a comparable mechanism operates in Merkel cell carcinoma (MCC), experimental models of oxidative stress were employed using hydrogen peroxide (H_2O_2)–treated Merkel cell cultures. Following four days of in vitro culture, the subcellular localization of Pax6 was markedly influenced by oxidative stress. In control conditions, Pax6 was predominantly localized within the nucleus. However, exposure to H_2O_2 at concentrations of 0.3 mM and 1.5 mM resulted in a pronounced exclusion of Pax6 from the nucleus and its redistribution to the cytoplasm. Quantitative analysis revealed that 99.6 ± 0.4% of Pax6/K8-positive Merkel cells exhibited nuclear Pax6 localization under control conditions (n = 250 cells from five independent replicates). In contrast, treatment with 0.3 mM H_2O_2 reduced nuclear localization to 23.94 ± 1.3%, with 76.06 ± 1.3% of cells showing cytoplasmic Pax6 (n = 250; one-way ANOVA, $P < 0.0001$). An even greater cytoplasmic shift was observed following exposure to 1.5 mM H_2O_2, where 95.06 ± 1.5% of Merkel cells demonstrated cytoplasmic Pax6 localization (n = 250; one-way ANOVA, $P < 0.0001$). The difference between the two oxidative stress conditions was statistically significant (t-test, $P < 0.001$), indicating a dose-dependent effect of H_2O_2 on Pax6 subcellular redistribution [85]. The observed nuclear translocation of Pax6 in Merkel cells after four days of in vitro culture suggests a potential role for this transcription factor in regulating postnatal Merkel cell maturation. In vivo observations support this notion, as Pax6 localization is predominantly cytoplasmic during prenatal stages but undergoes significant nuclear translocation after birth. Cytoplasmic Pax6 in vivo appears to contribute to Merkel cell differentiation by regulating structural markers such as keratin 8 (K8). This regulation may occur either through residual nuclear Pax6 activity sufficient to maintain K8 gene expression or via non-genomic functions of Pax6. Notably, studies using Pax6-deficient ($Pax6^{-/-}$) models indicate that Pax6 is not essential for the expression of keratin 20 (K20), a marker of fully differentiated Merkel cells. Nucleocytoplasmic trafficking of Pax6 is a tightly controlled process governed by multiple regulatory mechanisms, among which the leucine-rich nuclear export signal (NES) pathway is the most extensively characterized. This export process requires the activity of the conserved transport receptor CRM1 and the small GTPase Ran, a member of the RAS superfamily. CRM1-mediated nuclear export is dynamically regulated through reversible masking and unmasking of the NES motif, often driven by post-translational modifications such as phosphorylation or oxidative disulfide bond formation. In silico structural analysis of the Pax6 protein has confirmed the presence of a functional leucine-rich NES motif, whose accessibility is dependent on conformational changes within adjacent protein domains [85]. Moreover, Pax6 expression correlates with alterations in its subcellular localization and modulation of catalase expression, suggesting a protective cellular response to oxidative stress. Regarding MCC, elevated oxidative stress has been associated with enhanced nuclear export of Pax6, further supporting its involvement in redox-sensitive regulatory mechanisms within tumor cells [85].

TGF-β and oxidative stress

ROS concentration in cells and lack of antioxidants and antioxidative pathways result in oxidative stress mechanisms eventually. Growth factor-beta (TGF-β). is increased therefore as an anti-tumorigenic agent in the first stages of cancers and the cause of epithelial-mesenchymal transition (EMT) triggers later in the aggressive phases. Furthermore (TGF-β) leads to ROS expression in tumor cells.[86]

Oxidative stress causes pax6 secretion. adding H2O2 to Pax6/k8 positive Merkel cell culture results in cytoplasmic relocalization of pax6 in Merkel cells in vitro after 4 days. Compare to pax6 nuclei localization in control cell culture, the different dosage of H2O2 shows different pax6 expression in the cell's cytoplasm. This simulation is conducted after pax6 relocalization in the adult eye's corneal epithelium cell and to monitor pax6 cytoplasmic and nuclear localization in Merkel cells in vivo [85].

Oxidative stress also results in ROS products which stimulate TGF-β1 release. TGF-β1 has a biphasic role in both oxidative stress suppression and its over-activation leading to tumor angiogenesis and thus its aggression. [86]

P62

p62 is a multifunctional adaptor protein that serves as a key substrate in the autophagy pathway. Recent evidence has demonstrated that p62 participates in the selective delivery of ubiquitinated proteins, including tau, to the proteasome for degradation. In addition to its role in proteostasis, p62 dynamically shuttles between the nucleus and cytoplasm, enabling the recognition and transport of ubiquitinated cargo and thereby contributing to both nuclear and cytosolic protein quality control mechanisms. Accumulation of p62 has been closely associated with increased oxidative stress, and sustained elevation of p62 levels has been shown to promote tumorigenic processes. In contrast, functional autophagy exerts tumor-suppressive effects by facilitating the degradation and clearance of p62 [87]. Consistent with these observations, defective autophagic activity has been identified in MCC tumor tissues as well as in primary human MCC-derived cell lines. Pharmacological inhibition of the mammalian target of rapamycin (mTOR) pathway in MCC cells results in pronounced growth arrest accompanied by enhanced autophagosome formation, highlighting the importance of autophagy regulation in MCC pathophysiology [88]. Moreover, oxidative stress induced by ultraviolet A (UVA; 320–400 nm) radiation promotes extensive protein oxidation, affecting key DNA repair components. Among the most vulnerable targets are proteins involved in nucleotide excision repair (NER), whose functional impairment under oxidative conditions compromises genomic stability. Given that NER plays a critical role in protecting cells from mutagenesis, its inhibition represents an important downstream consequence of oxidative stress [89]. Members of the Bcl-2 protein family are central regulators of apoptotic signaling, and their activity is tightly modulated through post-transcriptional and post-translational mechanisms, including phosphorylation, dimerization, and proteolytic processing. Experimental studies using adult cardiac myocytes have shown that oxidative stress–activated kinase signaling pathways can influence both the expression level and phosphorylation status of Bcl-2, thereby altering its anti-apoptotic function. Exposure of cardiac myocytes to 0.2 mM H_2O_2, a condition known to induce apoptosis, led to a marked reduction in total Bcl-2 protein levels accompanied by increased Bcl-2 phosphorylation. Notably, inhibition of the p38 mitogen-activated protein kinase (p38 MAPK) pathway attenuated Bcl-2 phosphorylation, whereas blockade of ERK1/2, JNK, or PI3K signaling produced no significant effect. These findings indicate that oxidative stress–mediated activation of p38 MAPK promotes Bcl-2 phosphorylation and subsequent degradation, ultimately impairing its anti-apoptotic activity [90].

In addition, the coexistence of oxidative DNA damage, as indicated by elevated levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG), and expression of the MCPyV large T antigen suggests a mechanistic link between ultraviolet-induced oxidative stress and viral oncogenesis. High 8-OHdG positivity in tumors harboring MCPyV large T antigen supports the notion that UV-mediated oxidative DNA damage and viral infection may synergistically contribute to MCC tumorigenesis [91, 92].

G6PD (Glucose-6-phosphate dehydrogenase)

G6PD is a cellular enzyme in the cytoplasm and its expression is increased in many cancers, including esophageal squamous cell carcinoma, and cervical cancer [93-94]. A major part of G6PD in cancer cells is protection against oxidative damage-induced cell death, which is regulated by the tumor suppressor gene p53, which is often mutated in MCC [95-96] (Table 1). Regarding the relationship between G6PD and MCC, G6PD protects the major part from cell death in MCC but it is supposed that because of its antioxidant effects, it can play a role against cancer [97-98]. However, G6PD is considered a protection against oxidative stress, an increase in G6PD amounts in response to the oxidative stress pathway can be a prognosis of tumor aggression and thus malignancy in multiple cancers including MCC. A rise in Oxidative stress due to the body's involvement with MCC leads to a rise in G6PD cell content to neutralize the oxidative stress effects and sustain the cell pathways balance as a result. Furthermore, G6PD results in tumor immunity increment and therefore resistance against immune system. On the other hand, low rates of G6PD represents positive approaches toward MCC treatment by increasing immune responses and obstacles tumor growth [10] (Table 1).

Discussion

Aerobic cells continuously generate reactive oxygen species (ROS) as byproducts of normal metabolic activity. At physiological levels, ROS

function as critical signaling molecules that regulate transcription factor activation, as well as cellular proliferation and differentiation processes [10]. In contrast, excessive or dysregulated ROS production disrupts redox homeostasis and results in oxidative stress (OS), which can trigger pathological outcomes such as apoptosis, autophagy, and necrotic cell death [99]. In vitro, cellular ROS levels are closely linked to metabolic activity, which in turn correlates with proliferation rate; rapidly dividing cells exhibit higher metabolic demands and consequently increased ROS generation [100]. Oxidative stress arises when ROS production exceeds the neutralizing capacity of antioxidant defense systems or when cells are exposed to exogenous oxidative stimuli. Under these conditions, an imbalance between pro-oxidants and antioxidants leads to the accumulation of damaging oxidizing agents. The human antioxidant defense network consists of enzymatic and non-enzymatic components [101]. Enzymatic antioxidants include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px), while non-enzymatic defenses comprise molecules such as glutathione (GSH), melatonin, and vitamin E [101]. Collectively, oxidative stress can be defined as a state in which excessive reactive oxygen and nitrogen species overwhelm the cellular antioxidant capacity, resulting in molecular and cellular damage [102]. Within this context, Pax6 has emerged as a critical regulator of Merkel cell biology. Pax6 plays a pivotal role in perinatal Merkel cell development and acts as a nucleocytoplasmic shuttling protein whose subcellular localization is sensitive to oxidative stress. As a tumor suppressor, Pax6 has been implicated in the regulation of Merkel cell growth, and its dysregulation may contribute to the initiation and progression of Merkel cell carcinoma (MCC) [85]. Epidemiological and clinical evidence further supports the role of environmental oxidative stressors in MCC pathogenesis, as increased risk has been associated with chronic sun exposure, UVA-based photochemotherapy, and the presence of other ultraviolet-related cutaneous malignancies [103, 104]. Oxidative DNA damage, commonly assessed

Table 1. This table consolidates the relationship between oxidative stress and various key molecules implicated in Merkel Cell Carcinoma (MCC). It highlights the role of Pax6, TGF-β, p62, Bcl-2, 8-OHdG, and G6PD in the pathophysiology of MCC, along with the experimental conditions and effects observed in vitro and in vivo. The references are cited to provide supporting evidence from relevant studies.

Mechanism/Protein	Effect of Oxidative Stress	Experimental Observation	Impact on MCC (Merkel Cell Carcinoma)	Key References
Pax6	Oxidative stress influences Pax6 localization by causing its cytoplasmic shift.	Exposure to 0.3 mM and 1.5 mM H_2O_2 leads to Pax6 exclusion from the nucleus.	Enhanced oxidative stress contributes to the redistribution of Pax6, which plays a role in Merkel cell differentiation.	[85]
TGF-β	Increased ROS and oxidative stress lead to the upregulation of TGF-β.	ROS products stimulate TGF-β1 release, which has both anti-tumorigenic and tumor-promoting roles.	TGF-β mediates oxidative stress-induced tumor progression, triggering epithelial-mesenchymal transition (EMT) in aggressive phases of MCC.	[86]
P62 (SQSTM1)	Increased oxidative stress promotes accumulation of p62.	p62 shuttles between the nucleus and cytoplasm, influencing tumorigenic processes.	Accumulation of p62 in MCC tissues is associated with defective autophagy, promoting tumorigenesis.	[87], [88]
Bcl-2	Oxidative stress activates kinases that phosphorylate and degrade Bcl-2.	0.2 mM H_2O_2 exposure leads to reduced Bcl-2 levels and increased phosphorylation.	Oxidative stress–mediated Bcl-2 degradation impairs anti-apoptotic functions, contributing to apoptosis in MCC cells.	[90]
8-OHdG	Oxidative stress causes DNA damage, indicated by increased levels of 8-OHdG.	Elevated 8-OHdG levels correlate with MCPyV T antigen expression, indicating DNA damage.	Oxidative DNA damage contributes to MCC tumorigenesis through UV-mediated oxidative stress and viral oncogenesis.	[91], [92]
G6PD (Glucose-6-phosphate dehydrogenase)	Protects cells from oxidative stress-induced damage.	Increased G6PD expression in response to oxidative stress neutralizes damage.	G6PD protects cells in MCC from oxidative damage and promotes tumor immunity, but its high levels correlate with tumor aggressiveness.	[93], [94], [95], [96], [97], [98]

by the biomarker 8-hydroxy-2′-deoxyguanosine (8-OHdG), appears to interact with viral oncogenic mechanisms in MCC. Elevated levels of 8-OHdG in tumors expressing the MCPyV large T antigen suggest a synergistic relationship between ultraviolet-induced oxidative stress and viral infection in MCC tumorigenesis [105, 106]. This interaction highlights the importance of redox imbalance in facilitating virus-associated malignant transformation. Glucose-6-phosphate dehydrogenase (G6PD), a cytoplasmic enzyme involved in maintaining cellular redox balance, is overexpressed in multiple malignancies, including esophageal squamous cell carcinoma and cervical cancer [97, 108]. In cancer cells, G6PD plays a central role in protecting against oxidative damage–induced cell death, a function that is tightly regulated by the tumor suppressor p53 [98, 109, 110]. Given that p53 mutations are frequently observed in MCC [111], dysregulation of G6PD-mediated redox control may contribute to tumor survival and progression. Reactive oxygen species are among the most common sources of DNA damage in both host and viral genomes. In the context of human papillomavirus (HPV) infection, viral replication has been shown to coincide with increased oxidative damage to viral DNA [105, 112]. Additionally, the HPV-encoded E6* protein directly enhances ROS production and promotes DNA damage [106]. Environmental and lifestyle-related oxidative stressors further exacerbate genomic instability. Factors such as cigarette smoking and co-infection with sexually transmitted pathogens, including Chlamydia trachomatis and Neisseria gonorrhoeae, have been linked to a higher incidence of HPV-associated malignancies [97,98,107–111]. An expanding body of evidence now supports a strong association between viral infections and oxidative stress in cancer progression [112-114]. Beyond HPV, numerous other viruses have been directly or indirectly implicated in oncogenesis [115]. One of the most critical mechanisms underlying virus-induced carcinogenesis is the insertion of viral DNA into the host genome, a process observed in infections caused by HPV, hepatitis B virus (HBV), and Merkel cell polyomavirus (MCPyV), all of which contribute to malignant transformation through genomic instability and dysregulated cellular signaling [1, 3, 12].

Conclusion

The findings presented in this study emphasize the profound role of oxidative stress in the pathogenesis of Merkel Cell Carcinoma (MCC), particularly through its influence on the subcellular localization of key regulatory proteins such as Pax6, TGF-β, p62, and Bcl-2. Oxidative stress-mediated shifts in Pax6 localization, from the nucleus to the cytoplasm, highlight its potential involvement in postnatal Merkel cell differentiation and its dysregulation in MCC. The interplay between oxidative stress and the upregulation of TGF-β underscores its biphasic role in both tumor suppression and promotion, particularly in the aggressive phases of cancer progression.

Furthermore, the accumulation of proteins like p62 and the modulation of G6PD expression reveal the complex cellular mechanisms that protect against oxidative damage while simultaneously contributing to tumorigenesis. The elevation of oxidative stress markers, such as 8-OHdG, further corroborates the critical role of oxidative DNA damage in MCC development, potentially facilitated by viral oncoproteins like MCPyV large T antigen.

Together, these findings underscore the need for a deeper understanding of oxidative stress pathways in viral-associated cancers like MCC. Targeting the regulatory mechanisms governing oxidative stress and its impact on protein localization and expression may offer novel therapeutic strategies for combating MCC. Future research should focus on the development of targeted therapies aimed at modulating oxidative stress and its associated pathways to prevent or treat MCC more effectively.

Data Availability Statement

N/A.

Conflict of Interest

Authors declare no conflict of interest.

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