

## Merkel Cell Polyomavirus

CAS No.: none assigned

Known to be a human carcinogen

Also known as MCV or MCPyV

### Carcinogenicity

Merkel cell polyomavirus (MCV) is known to be a human carcinogen based on sufficient evidence from studies in humans. This conclusion is based on evidence from epidemiological, clinical, and molecular studies, which show that MCV causes Merkel cell carcinoma, and on supporting mechanistic data. MCV causes cancer by integration of the viral DNA into the host-cell genome and expression of two MCV proteins: small T (sT) antigen and a mutated form of large T (LT) antigen. Only the mutated, integrated form of MCV is associated with carcinogenicity. Merkel cell carcinoma is more common in people infected with human immunodeficiency virus type 1 (HIV-1) and in organ-transplant patients than in people with normal immune function, suggesting that immunosuppression is an important cofactor in MCV carcinogenesis.

### Cancer Studies in Humans

Evidence for an association between MCV infection and Merkel cell carcinoma is based on consistent findings of increased risk in epidemiological studies of populations in different geographical areas, a suggestion of a dose-response relationship, and the findings of clinical and molecular studies. Although MCV infection is common, Merkel cell carcinoma is rare; it is a highly aggressive form of skin cancer most common in elderly Caucasian men and in immunosuppressed individuals (such as organ-transplant recipients and people infected with HIV-1) (Engels *et al.* 2002, Schrama *et al.* 2012, Clarke *et al.* 2015).

Three case-control studies (Carter *et al.* 2009, Paulson *et al.* 2010, Viscidi *et al.* 2011) and one nested case-control study (Faust *et al.* 2014) found statistically significant associations between MCV infection (as measured by antibodies against MCV viral molecules) and Merkel cell carcinoma, with odds ratios (ORs) ranging from 4.4 to 63.2. In the nested case-control study (Faust *et al.* 2014), the findings of an association of Merkel cell carcinoma with high levels of anti-MCV antibodies (immunoglobulin G [IgG] antibodies that bind to the virus) or MCV-neutralizing activity (due to antibodies that inhibit infectivity) were mainly limited to women; however, there were few men in this study. The OR was higher among all individuals with high levels of anti-MCV IgG antibodies (OR = 4.3, 95% confidence interval [CI] = 1.3 to 17.4) than among all individuals with any level of MCV IgG antibodies (OR = 2.6, 95% CI = 0.7 to 15.0) (the analysis did not stratify by antibody level), providing limited support for a dose-response relationship. This prospective study also demonstrated a temporal relationship between MCV infection and the onset of Merkel cell carcinoma. Because of the paucity of studies and absence of known risk factors for MCV infection in relation to Merkel cell carcinoma, confounding and chance cannot be ruled out as possible explanations for the results of these epidemiological studies.

Clinical and molecular studies provide strong evidence that MCV has an important causal role in Merkel cell carcinoma (see Studies on Mechanisms of Carcinogenesis). MCV antibody levels were significantly higher in MCV-positive Merkel cell carcinoma patients than in healthy individuals infected with MCV, which suggests that development of Merkel cell carcinoma is preceded by an unusually robust MCV infection (Pastrana *et al.* 2009, Agelli *et al.* 2010). In case-series studies (21 studies with over 850 cases of Merkel cell carcinoma),

MCV has been detected in approximately 80% of cases (IARC 2013, NTP 2016), suggesting that there are two forms of Merkel cell carcinoma, the majority occurring in MCV-positive individuals and the minority in individuals not infected with MCV (Moore and Chang 2014). However, other studies have suggested that MCV is involved in most or all cases of Merkel cell carcinoma (Carter *et al.* 2009, Rodig *et al.* 2012).

MCV DNA is integrated into the host genome in primary Merkel cell tumors and metastases, and the DNA integration site is the same in all cells of the tumor and its metastases in a given individual. This monoclonal integration of MCV DNA provides strong evidence that viral infection precedes proliferation of the original cancer cell (Feng *et al.* 2008, Laude *et al.* 2010) and that MCV is not an incidental or passenger infection in Merkel cell carcinoma (Kuwamoto 2011, Chang and Moore 2012).

### Studies on Mechanisms of Carcinogenesis

MCV-associated cancer is thought to develop through a complex process that involves interactions among many viral, host, and environmental factors. Although MCV infection is common, very few people develop Merkel cell carcinoma (Chang and Moore 2012, IARC 2013). Data from molecular studies have shown that host cells infected with the episomal (non-integrated) form of the virus are not transformed; only the integrated and mutated form of MCV is associated with cancer (Moore and Chang 2014). Exposure to ultraviolet radiation or other environmental mutagens may increase the likelihood of the mutations that transform symptomless viral infection into cancer (Moore and Chang 2010).

The key events in induction of Merkel cell carcinoma by MCV include immunosuppression and immune evasion, monoclonal integration of the MCV genome into the host-cell DNA, mutations causing truncation of the LT antigen, production of T antigens in tumor cells, and impaired regulation of the cell-division cycle and apoptosis (programmed cell death) (Moore and Chang 2010). Truncation of the LT antigen, which prevents the virus from replicating, is a signature feature of all MCV-positive Merkel cell carcinoma. *In vitro* and *in vivo* studies have clearly demonstrated that both the mutated LT antigen and another T antigen (sT) are required for transformation of the host cell into a cancer cell and for proliferation and survival of the cancer cells (Moore and Chang 2010, Shuda *et al.* 2011, Schmitt *et al.* 2012, Borchert *et al.* 2014, Stakaityte *et al.* 2014). Moreover, these antigens are produced only in MCV-infected tumor cells and are found in most Merkel cell carcinoma samples (for more information, see NTP 2016).

### Biological Properties

Merkel cell polyomavirus is a very stable non-enveloped DNA virus found in the skin, and it is integrated into the DNA of most Merkel cell tumors (Moore and Chang 2010, Carter *et al.* 2013, Dalianis and Hirsch 2013, IARC 2013, Spurgeon and Lambert 2013, Moens *et al.* 2015). The structure of the MCV is simple, consisting of two capsid (shell) proteins with a circular 5-kb DNA genome that wraps around structural histone (DNA packaging) proteins derived from the host cell (Dalianis and Hirsch 2013, IARC 2013, Spurgeon and Lambert 2013, Moens *et al.* 2015). Once MCV has entered a host cell, its DNA is maintained in a form that allows it either to replicate independently or to integrate into the host cell's DNA for replication (IARC 2013). MCV can exist in either a lytic phase (in which the infected cell is destroyed and viral particles are released) or a latent phase (in which the virus does not replicate). During the latent phase, little viral gene expression occurs, and the virus can evade immune detection.

## Detection

MCV infections can be detected in body fluids (blood, saliva, or urine) by the presence of anti-MCV antibodies or by polymerase chain reaction (PCR) amplification of the viral DNA and in tissue (skin, mouth, liver, or Merkel cell tumors) by the presence of viral antigens or DNA (Moore and Chang 2010, Dalianis and Hirsch 2013, IARC 2013, Moens *et al.* 2015). The rates at which MCV DNA has been detected in skin samples have been reported to be up to 28% by standard or nested PCR, 40% by rolling circle DNA amplification, and 100% by real-time or quantitative PCR (IARC 2013). MCV DNA detection rates in the oral cavity have been reported to range from 8.3% to as high as 60%. Some studies have detected MCV DNA at higher rates in the oral-cavity mucous membranes than on the skin, while others have reported the opposite, possibly because of differences in sampling methods (e.g., biopsies vs. surface swabs). MCV DNA found on one area of the skin is genetically identical to MCV found on other areas of skin. The level of anti-MCV antibodies in the blood correlates with viral load on the skin and with active viral shedding.

## Exposure

Studies measuring antibodies to MCV have shown that a significant number of people in the United States are infected with MCV. Reported U.S. MCV seroprevalence rates have ranged from 23% to 88% (Carter *et al.* 2009, Kean *et al.* 2009, Pastrana *et al.* 2009, Tolstov *et al.* 2009, 2011, Viscidi *et al.* 2011). Age-specific MCV seroprevalence has been reported to be 20% in children aged 1 to 5 years, 35% to 50% in those under 10 to 15 years old, and 46% to 87.5% in adults (Tolstov *et al.* 2009, Chen *et al.* 2011, Viscidi *et al.* 2011, IARC 2013). MCV may be undetectable in newborns (Gustafsson *et al.* 2012).

## Transmission

Transmission of MCV is not fully characterized (IARC 2013). The skin appears to be a primary site of MCV infection, and healthy individuals have been shown to chronically shed MCV DNA from the skin surface (Schowalter *et al.* 2010). Possible transmission through close personal contact via saliva or skin between young siblings and between mothers and their children is suggested by a study in Cameroon, Central Africa (Martel-Jantin *et al.* 2013), and a cross-sectional study of a large rural Chinese population found that poor personal hygiene (e.g., infrequent bathing) may increase the risk of cutaneous transmission of MCV via frequent close contact or shared family environment (Zhang *et al.* 2014). MCV DNA has also been detected in saliva, the mouth, the esophagus, and the colon (Loyo *et al.* 2010) and in nasal mucus samples, tonsils, lung tissue, and secretions in the lower respiratory tract (IARC 2013), suggesting possible transmission via the digestive tract (e.g., fecal-oral transmission) and respiratory tract. Reports of detection of MCV DNA in blood or urine have been inconsistent; a few studies have found MCV at low levels in small percentages of the samples (IARC 2013). Because most adults have MCV antibodies, blood is not expected to play a large role in transmission, and the low levels of MCV reported in urine could be due to contamination from skin during passing of urine. MCV has been detected in urban sewage (Spurgeon and Lambert 2013) and in 85% of environmental surface samples (Foulongne *et al.* 2011, IARC 2013). It is stable at temperatures up to 167°F, suggesting that virus present in the environment may remain viable and be a source of infection.

## Diseases (Non-Cancer), Prevention, and Treatment

MCV establishes a chronic lifelong, symptomless infection in a large majority of healthy individuals, but it has not been associated with any disease or symptoms other than Merkel cell carcinoma (IARC 2013). Some treatments of MCV-positive Merkel cell carcinoma tar-

get MCV T antigens (Samimi *et al.* 2015). There is no vaccine against MCV (CDC 2015, FDA 2015), but limited vaccine development efforts are ongoing (Pastrana *et al.* 2009, Zeng *et al.* 2012, Gomez *et al.* 2013, Samimi *et al.* 2015).

## Regulations

### Department of Transportation (DOT)

Infectious substances are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

### Occupational Safety and Health Administration (OSHA)

First-aid training program trainees must have adequate instruction in the value of universal precautions for preventing infectious diseases.

## Guidelines

No specific guidelines relevant to reduction of exposure to MCV were identified.

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