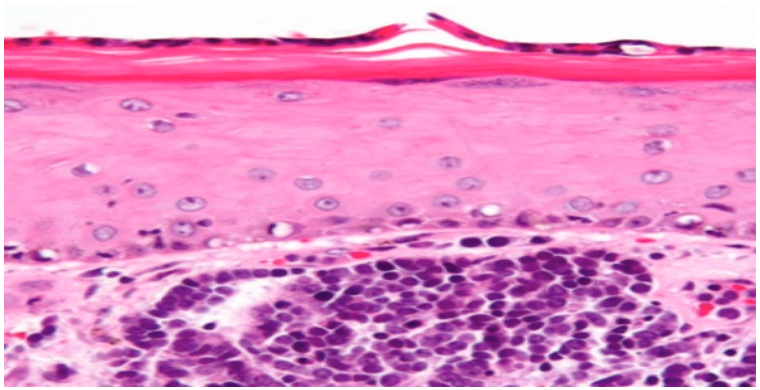
NTP
National Toxicology Program

Draft RoC Monograph
Merkel Cell Polyomavirus



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NTP Peer Review Meeting
December 17, 2015

Outline

Properties and exposure

Mechanistic information

Human cancer studies

Preliminary level of evidence summary

Properties and Significant U.S. Exposure

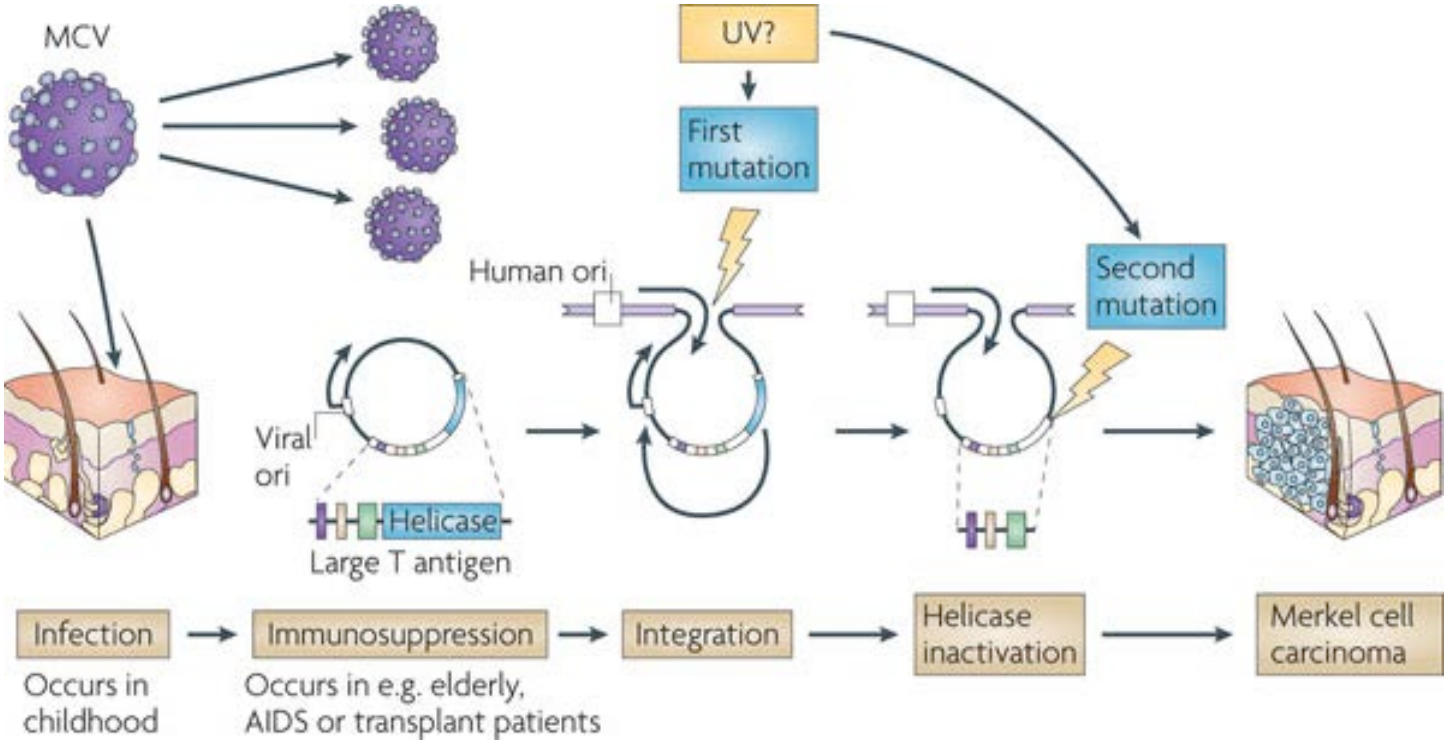
- Double stranded DNA virus, non-enveloped
- Part of normal skin flora, also detected in saliva
- Asymptomatic life-long infection in healthy individuals
- Although called Merkel cell virus, cellular origin of infection uncertain
- U.S. MCV seroprevalence rates reported as 20% in 1-5 yr olds, 35-50% in 10-15 yr olds, and 46-88% in adults
- Mode of transmission unknown – possibly through close contact of family members or from environmental sources

Assessment of Three Cancer Endpoints

- Merkel cell carcinoma
- Lung carcinoma
  - Inconsistent evidence, inadequate to assess.
- Chronic lymphocytic leukemia
  - Inconsistent evidence, inadequate to assess.

Key Events Leading to Merkel Cell Carcinoma

At least two mutations are needed to transform cells: integration of viral genome and large T antigen truncation

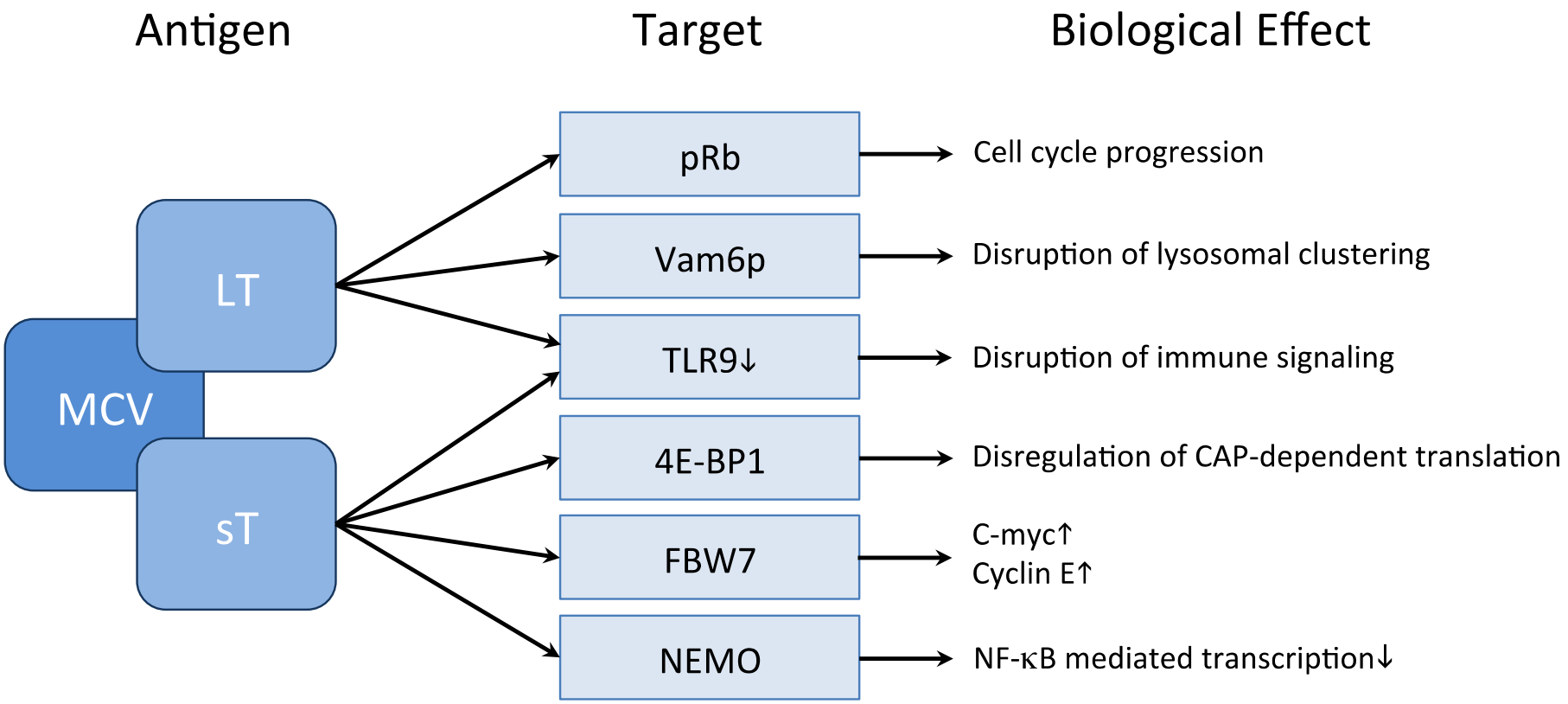


Moore and Chang (2012) *Nature Reviews Cancer* 10(12): 878-889.

MCV T-antigens transform cells *in vivo* and *in vitro*

- Expressed in MCV-infected tumors, and both antigens required to maintain tumor growth and survival
  - siRNA: reducing sT prevented proliferation of MCC; reducing sT and LT resulted in necrosis of MCV positive MCC
- MCV T antigens have oncogenic activity in transgenic mice
  - MCC derived truncated LT and sT antigens promoted skin neoplasias; sT expression alone sufficient for skin transformation

Truncated LT and sT Biological Effects



pRB = retinoblastoma protein, Vam6p = vacuolar protein-sorting gene product, TLR9 = Toll-like receptor 9, 4E-BP1 = eukaryotic translation initiation factor 4E-binding protein 1, FBW7 = F-box/WD repeat-containing protein 7, NEMO = NF-κB essential modulator. Adapted from White *et al.* 2014.

Sufficient level of evidence from human studies

Epidemiology	21 case-series (716 MCV/855 MCC cases)
Studies with positive associations or dose-response	3/3 case-control studies; moderate to high statistically significant OR
	1 nested case-control study – statistically significant increase in risk in females but only modest non-significant risk in males
Human tissue	
Clonality	Monoclonal
% MCV-infected tumors	>80% of MCC
MCV protein expression	Truncated Large T (LT) 75% of MCC
	Small T (sT) antigen 92% of MCC

OR = odds ratio.

MCV Preliminary Level of Evidence Summary

- Sufficient evidence for Merkel cell carcinoma
  - Moderate to high significant ORs in 3/3 case-control studies
  - Monoclonal integration
  - Express sT and truncated LT antigens
- Key mechanistic studies
  - Truncated LT and sT required to maintain growth and survival of human tumors
  - MCV T antigens have oncogenic activity in transgenic mice

Clarifications?

Peer Reviewer Comments

All sections: Comment on whether the information is clear and technically accurate and identify any information that should be added or deleted,

Properties, Detection and Human Exposure

- and whether adequate information is presented to document past and/or current human exposure.

Human Cancer Studies

- and provide any scientific criticisms of NTP's cancer assessment of the epidemiologic studies of exposure to the virus.

Mechanistic and Other Relevant Data

- and provide any scientific criticisms of the NTP's synthesis of these data assessing effects of the virus.

Level of Evidence Conclusion (Vote)

Sufficient evidence of carcinogenicity from studies in humans

- Cancer sites with sufficient evidence
  - Merkel cell carcinoma

Preliminary Listing Recommendation (Vote)

MCV

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.

Draft Substance Profile

- Contains NTP's preliminary recommendation of the listing status of the substance
- Summarizes the scientific information that is key to reaching a recommendation
- Provides information on properties, use, production, and exposure
- Provides information on existing federal regulations and guidelines

Peer Reviewer Comments

- Provide any new comments (e.g., not previously provided on the same facts or issues in the cancer hazard evaluation section) on whether the informtion on properties and detection, human exposure, cancer studies in humans and mechanistic data is clear and technically accurate.
- Comment on whether the substance profile highlights the information on cancer studies in humans and mechanistic data that are considered key to reaching the listing recommendation.