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Role of Merkel cell polyomavirus Small Tumour antigen in the development and metastatic potential of Merkel cell carcinoma

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Merkel cell carcinoma (MCC) is an aggressive skin cancer with a high likelihood of recurrence and metastasis. The number of reported cases of MCC has tripled in the past 20 years, and risk factors include advanced age, UV exposure, and immune suppression. MCC has a very poor 5-year survival rate, characterised by local recurrence, early spread to local lymph nodes and high likelihood of forming distant metastases. Merkel cell polyomavirus (MCPyV) is associated with the majority of MCC cases, and MCPyV-induced tumourigenesis largely depends on the expression of the small tumour antigen (ST). However, as MCPyV was only discovered in 2008, little is known about potential links between MCPyV T antigen expression, tumourigenesis and the highly metastatic nature of MCC. Here we have utilised a SILAC-based quantitative proteomic approach to examine the global changes on the host cell proteome upon MCPyV ST expression. Results demonstrate that MCPyV ST expression affects both the microtubule network and actin cytoskeleton enhancing cell motility. We specifically show that MCPyV ST destabilises the microtubule network and also promotes the formation of actin-based protrusions reminiscent of filopodia, and show that this action is facilitated by the catalytic subunit of protein phosphatase 4 (PP4C). Moreover, MCPyV ST-induced cell motility is dependent upon the activity of Rho-family GTPases Cdc42 and RhoA. In addition, our results indicate that the MCPyV ST-PP4C interaction results in the dephosphorylation of β 1 integrin, likely contributing to the activation of the cell motility pathway upon MCPyV ST expression. These findings describe a novel mechanism by which a human tumour virus induces cell motility, which may ultimately lead to cancer and metastasis. As such it may have implications for the potential future therapeutic targets for disseminated MCC.