

# "Selectin" to Evade the Immune Response

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Merkel cell carcinoma (MCC) is an aggressive and lethal skin cancer caused by Merkel cell polyomavirus (MCPyV). The presence of CD8+ cytotoxic T cells in these tumors is correlated with survival, perhaps because MCPyV oncoproteins expressed in these tumors are targets for the immune response. However, only ~20% of patients with MCC have CD8+ T cells present in their tumors. In a recent study published in the *Journal of Investigative Dermatology*, Drs. Olga K. Afanasiev (University of Washington) and Paul Nghiem (University of Washington and Clinical Research Division) along with an international team of collaborators identify a possible mechanism for the low incidence of CD8+ T cells in these tumors. The authors demonstrate that E - selectin, a molecule involved in CD8+ T cell migration from blood vessels into skin, is downregulated in most MCCs, suggesting that current therapies modulating E - selectin expression may be useful in MCC treatment.

For a CD8+ T cell to enter the tumor, it must undergo a process called extravasation. Inflammation increases the expression of integrins, such as E - selectin, on cells lining the blood vessel lumen. Circulating CD8+ T cells recognize and bind these integrins (adhesion), then migrate out of the blood vessel following a chemokine gradient (transmigration). Once they are out of the blood vessel and in the tumor itself, CD8+ T cells recognize tumor - specific antigens and mediate a cytotoxic immune response.

Previous studies have demonstrated that squamous cell carcinoma evades the immune response by downregulating E - selectin expression (Clark, et al., 2008). To determine if MCC behaves in a similar manner Afanasiev et al., stained serial sections of MCC tumors with E - selectin specific antibodies, and found a 4 - fold reduction in E - selectin positive blood vessels within the tumor periphery compared to surrounding tissue ( $p < 0.05$ ). Furthermore, patient survival was positively correlated with increased expression of E - selectin within the tumor. Consistent with E - selectin's importance in extravasation, the authors found very low or no CD8+ T cell infiltrate in 75% of the MCC they examined.

Local nitric oxide (NO) production has been shown to downregulate vascular E - selectin (Gehad et al., 2012). Afanasiev et al., stained for nitrotyrosine, a byproduct of local NO production, in MCC serial sections and found that 43% of tumors had moderate to high nitrotyrosine levels, while in only

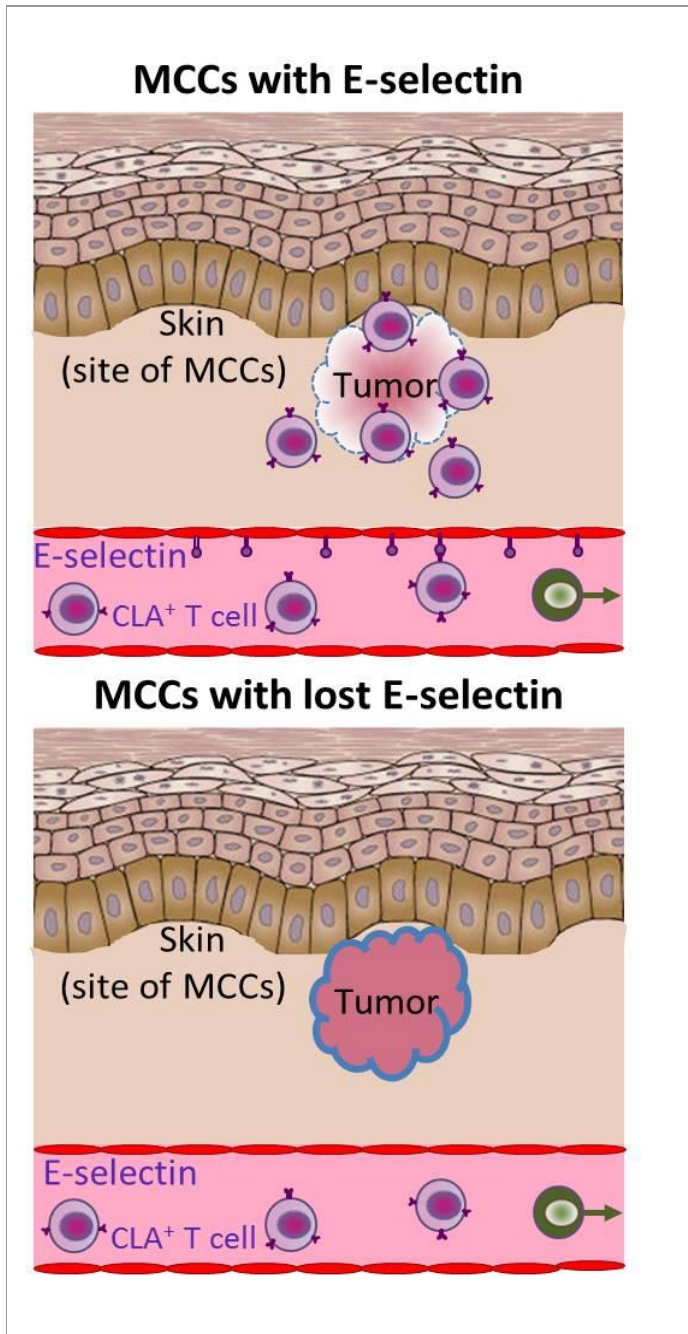
6% of tumors nitrotyrosine was absent. In addition, nitrotyrosine levels were negatively correlated with E - selectin expression in intratumoral blood vessels ( $p < 0.05$ ). Taken together, these data suggest that local production of NO may be one mechanism that MCC downregulates E - selectin and excludes CD8+ T cells from the tumor.

CD8+ T cells have the potential to control tumor progression, and this study identifies one mechanism by which MCC may regulate the tumor microenvironment to prevent CD8+ T cells from entering the tumor. Importantly, while increased E - selectin is associated with better prognosis for patients with MCC, in some other cancers E - selectin is a marker for increased metastatic potential, suggesting that drugs which modulate E - selectin levels in blood vessels may be useful only in certain tumors, such as MCC. "Therapeutic manipulation of the proposed mechanisms of T cell evasion will help establish the causation and clinical relevance of these findings in MCC patients. Furthermore, it may be appropriate to combine such treatment with adoptive virus - specific T - cell therapy to improve migration of T cells into tumors and thereby augment the efficacy of future immune therapy," according to Dr. Afanasiev.

[Afanasiev OK, Nagase K, Simonson W, Vandeven N, Blom A, Koelle DM, Clark R, Nghiem P.](#) 2013. Vascular e - selectin expression correlates with CD8 lymphocyte infiltration and improved outcome in merkel cell carcinoma. *J Invest Dermatol.* 133(8):2065 - 73.

See also: [Clark RA, Huang SJ, Murphy GF, Mollet IG, Hijnen D, Muthukuru M, Schanbacher CF, Edwards V, Miller DM, Kim JE, Lambert J, Kupper TS.](#) 2008. Human squamous cell carcinomas evade the immune response by down - regulation of vascular E - selectin and recruitment of regulatory T cells. *J Exp Med.* 205(10):2221 - 34.

See also: [Gehad AE, Lichtman MK, Schmults CD, Teague JE, Calarese AW, Jiang Y, Watanabe R, Clark RA.](#) 2012. Nitric oxide - producing myeloid - derived suppressor cells inhibit vascular E - selectin expression in human squamous cell carcinomas. *J Invest Dermatol.* 132(11):2642 - 51.



*Image courtesy of Dr. Olga K. Afanasiev*

Schematic of CD8+ T cell infiltration of Merkel cell carcinoma in the presence of E - selectin (top), or the exclusion of CD8+ T cells by downregulating E - selectin (bottom).