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Spotlight

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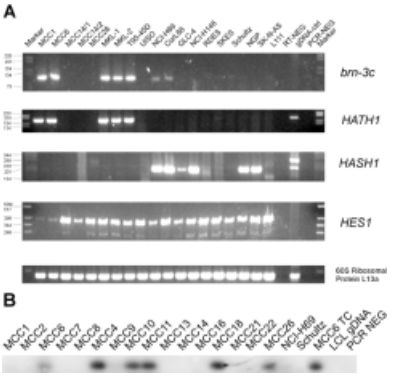
IN THIS ISSUE

IT HATH A GOOD PROGNOSIS

Brn-3c, a member of the POU-IV family of transcription factors, and HATH1, the human ortholog of the *Drosophila* basic helix-loop-helix transcription factor *atonal*, regulate cell fate and maintain the neuroendocrine phenotype in Merkel cell carcinomas, propose Leonard *et al.* (pages 103–110).

Merkel cells are slow-acting mechanoreceptors providing sensory information for touch and hair movement. Merkel cell carcinoma (MCC) is a rare, particularly malignant type of skin cancer. It is characterized by a significant rate of local recurrence (30–45%), early involvement of the locoregional lymph nodes (40–70%); and distant metastases (30–50%). Due to its aggressiveness and benign clinical appearance, the prognosis of this neoplasm is poor, with 25–30 % of patients dying within 3 years. A better understanding of the underlying biology may allow the development of new and better treatments.



Expression of proneuronal and proneuroendocrine transcription factors in MCCs.

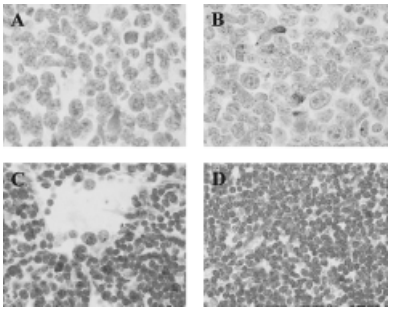
In earlier studies, the authors isolated a novel DNA binding complex in MCC cell lines, which they named Merkel nuclear factor (MNF). Now, they have identified one component of MNF as the proneuroendocrine transcription factor Brn-3c and demonstrated that all normal Merkel cells, but only a subset of MCC biopsies, express Brn-3c. The same holds true for HATH1, the human ortholog of the *atonal* family member MATH1, which is required for the proper development of murine Merkel cells.

The observed correlation between the expression of HATH1 and the retention of a neuroendocrine phenotype hints at the absence of Brn-3c and HATH1 expression as potentially useful prognostic markers for the identification of tumors that warrant aggressive treatment and closer follow-up.

IDO PUTS A DAMPER ON T CELLS

More often then not, the presence of T cells specific for tumor-associated antigens fails to diminish established tumors. Indoleamine 2,3-dioxygenase (IDO) is one reason, found Friberg *et al.* It helps tumors evade the host's immune system by locally inhibiting T cell-mediated rejection (pages 151–155).

The tumor microenvironment plays an interactive role in the host's immune system. So far, the expression of Fas ligand and the secretion of TGF-β and IL-10, among others, have been identified as players. But since these mechanisms are probably only relevant in a small fraction of tumors, researchers have continued looking for other mechanisms that enable tumors to evade the host's immune response.



IDO is expressed by mononuclear cells invading LLC tumors and tumor-draining lymph nodes.

IDO seems to fit their profile. The γ-interferon-inducible enzyme catalyzes the oxidative cleavage of tryptophan, an amino acid essential for the proliferation of T cells. This is nicely illustrated in placenta, where IDO expression helps to prevent allorejection of fetuses by maternal T cells.

When the authors transplanted Lewis lung carcinoma (LLC) into syngeneic C57BL/6 mice, they found evidence for the expression of IDO in mononuclear cells that had invaded growing tumors and tumor-draining lymph nodes. When they administered 1-methyl tryptophan, a competitive inhibitor of IDO, LLC tumor growth was markedly delayed *in vivo* and the allogeneic T cell response received a boost when tested *in vitro*.

Immunotherapeutic strategies designed to prime anti-tumor T cells produced only modest results when put to test in clinical trials. IDO inhibitors could lend tumor vaccines a helping hand in the future and improve their efficacy.

THE DARK SIDE OF THE GREAT OUTDOORS

All and sundry know that excessive sunbathing comes with an increased risk of cutaneous melanoma. Researchers suspected a similar association between sun exposure and ocular melanoma but evidence was patchy. Now, Vajdic *et al.* have established sun exposure as an independent risk factor for ocular melanoma (pages 175–182).

The authors enrolled 290 patients and 893 matched controls in a population-based case control study to tease out a possible connection. Their results indicate that the risk of choroidal and ciliary body melanoma correlates most strongly and consistently with the amount of time spent outdoors during weekdays but also, albeit to a lesser degree, with total outdoor hours. For men, a rural residence, a history of farming, or a previous diagnosis with cutaneous melanoma or cataract also confer an increased risk.

Extensive weekday sun exposure during the first 40 years of life had a major impact as had lifetime occupational exposure to sunlight. The bad news is that the authors didn't find evidence of protection from wearing sunglasses, probably because they often only provide incomplete protection. But the good news is that time outdoors on holidays, weekends, or during recreational activities doesn't increase the risk of ocular melanoma.

The authors point out that wrap-around sunglasses with UV-absorbing lenses and a wide-brimmed hat provide the best protection.

A NEW PALLIATIVE APPROACH

Intraperitoneal bispecific antibody (bsAb) therapy holds great promise as a palliative treatment in patients with recurrent ascites arising from ovarian carcinoma, report Marmé *et al.* (pages 183–189).

Women suffering from advanced stage ovarian or mammary carcinoma frequently develop malignant ascites or pleural effusions consisting of tumor cells and tumor-associated lymphocytes (TALs). Improving quality of life is a great challenge since only a few palliative strategies are available for these patients.

Previously the authors have shown that TALs residing in the peritoneal cavity of women with ovarian carcinoma are in an activated state and can lyse autologous tumor cells in the presence of the bsAb HEA125xOKT3 *in vitro* without further stimulation. BsAb HEA125xOKT3 recognizes EGP-2 or Ep-CAM antigen that is overexpressed on epithelial tumor cells and the epsilon-chain of the lymphocyte antigen CD3. Based on their earlier findings Marmé *et al.* reasoned that interperitoneal application of bsAb HEA125xOKT3 might induce tumor cell lysis *in vivo*.

Ten ovarian carcinoma patients presenting with malignant ascites resistant to chemotherapy received weekly intraperitoneal injections of 1mg bsAbs. In eight patients the treatment inhibited ascites production completely and partially in the other two. The therapy, which was generally well tolerated with only minor side effects, also reduced or stabilized the tumor marker CA125 in eight patients.

This novel strategy takes advantages of the cytotoxic capacity of bsAb-guides TALs and avoids the expensive and time-consuming expansion of effector cells in the lab. Hence, even in institutions without cell culture facilities ovarian cancer patients with advanced disease could soon profit from the beneficial palliative effect of intraperitoneal bsAb therapy.

WNT AND ITS ROLE IN MEDULLOBLASTOMA

Yokota *et al.'s* analysis points to the Wnt signaling pathway as an important contributor to the oncogenesis of sporadic medulloblastoma (pages 198–201).

The initial lead came from Turcot syndrome, a hereditary condition characterized by colon carcinomas and medulloblastomas. Most Turcot patients carry a germline mutation in a gene called APC, which negatively regulates β-catenin, an important player in the Wnt pathway. When APC is lost or inactivated by mutation, β-catenin is stabilized, resulting in accumulation of the protein that promotes cell proliferation.

Yokota *et al.* looked for elevated protein levels of β-catenin and Wnt-1 in sporadic medulloblastomas to confirm the role of the Wnt pathway in non-hereditary cases. Five of 23 (22%) tumors showed elevated levels of β-catenin. In 4 of these 5 cases either Wnt-1 overexpression or point mutations in regulators of β-catenin stability explained the accumulation.

Studies with larger sample sizes will be necessary to reveal the full extent of the Wnt pathway's contribution to the oncogenesis of medulloblastomas. It might be worthwhile to look for mutations in two mismatch repair genes, hMLH1 or hPMS2, both of which have been implicated in a number of Turcot syndrome patients where APC was unaffected.