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MODERN PATHOLOGY

Fishing for driver genes of peritoneal mesothelioma

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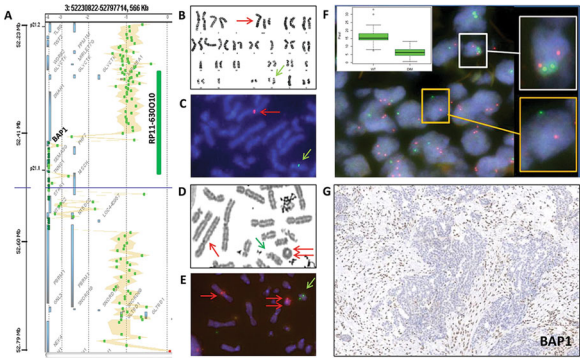

Fluorescence in situ hybridization (FISH) was performed on 75 formalin-fixed paraffin-embedded peritoneal mesotheliomas. This allowed Brich et al. to recognize two types of monoallelic loss and two types of biallelic loss/deletion in the target tumor suppressor genes *BAP1*, *CDKN2A*, and *NF2*. Distinct staining patterns were revealed for the different genes in the study, and these signals could be correlated with loss of expression immunophenotypes. *BAP1* hemizygous deletion, but not monosomy, was also invariably associated with loss of protein expression, whereas neither type of *CDKN2A* monoallelic loss correlated with p16 or MTAP immunohistochemistry. They went on to perform array comparative genomic hybridization, which further supported their FISH data, going so far as to identify two new driver genes: *SETD7* and *PCGF5*. Understanding more about the epigenetic relevance of these genes in peritoneal mesothelioma provides avenues for research into the development and possible treatment of the disease.

VISTA as a novel therapeutic target for mesothelioma

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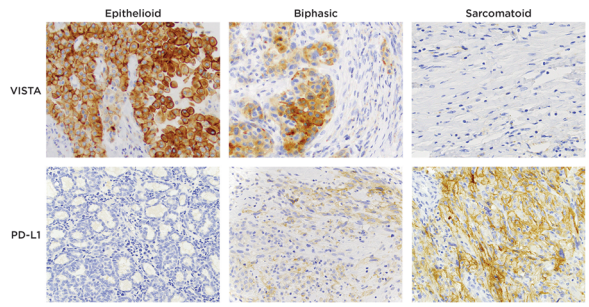
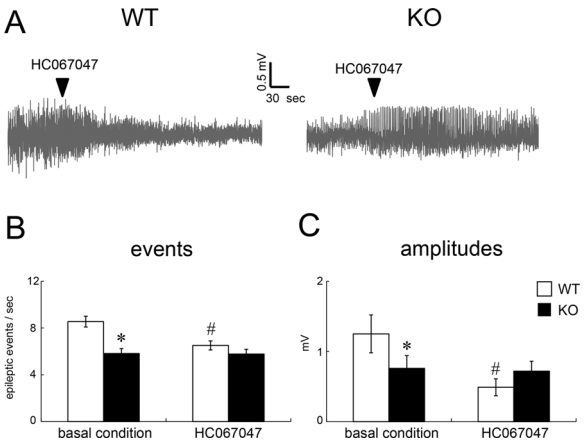


VISTA is an immune checkpoint gene that inhibits anti-tumor immune responses and is highly expressed in pleural mesothelioma, a disease type that does not to respond to anti-programmed cell death ligand 1 (PD-L1)/cytotoxic T lymphocyte–associated protein 4 (CTLA4) therapy. Comparing expression of VISTA and PD-L1 in a wide range of these tumors revealed multiple expression patterns. All (100%) of the benign mesotheliomas expressed VISTA, and 88 and 33% of epithelioid, 90 and 43% of biphasic, and 42 and 75% of sarcomatoid mesotheliomas expressed VISTA and PD-L1, respectively. On multivariable analysis, VISTA and PD-L1 expression in mesothelioma was associated with, respectively, better and worse overall survival, regardless of histology. These findings suggest VISTA's potential as a therapeutic target for this disease type.

LABORATORY INVESTIGATION

Targeted brain cooling as a therapeutic for epilepsy

https://doi.org/10.1038/s41374-019-0335-5



Shibasaki et al. have developed several novel devices for cooling specific regions of the brain in vivo and for measuring temperature of distinct regions of the brain in real time. Using the first device to specifically cool the hippocampus in normal mouse brain, they found that transient receptor potential cation channel V4 (TRPV4) was constitutively activated. Then they obtained electroencephalograms (EEGs) in a model of partial epilepsy, in both wild-type and TRPV4-deficient mice. The frequency of epileptic EEGs in wild-type mice was significantly higher than in the knockout mice, indicating a role for TRPV4 in epilepsy. The authors' second device showed that brain temperature was dramatically higher in

epileptic regions than in normal regions and that this temperature elevation was crucial for disease propagation. They propose cooling treatments targeted at epileptogenic foci as a therapeutic, as cooling might suppress neuronal discharges through inhibition/inactivation of TRPV4.

TRPM7 as a possible target for managing sepsis

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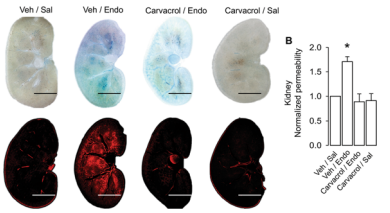
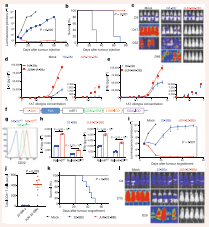


Transient receptor potential melastatin 7 (TRPM7) was investigated for its potential participation in renal vascular hyperpermeability, renal dysfunction, and enhanced mortality induced by endotoxemia. Endotoxin increased endothelial hyperpermeability and Ca^{2+} overload through the TLR4/NOX-2/ROS/NF-κB pathway. In vivo experiments revealed that under endotoxin stimulation, TRPM7 mediates endothelial cell Ca^{2+} overload, TLR4/NOX-2/ROS/NF-κB activation, VE-cadherin downregulation, and vascular monolayer disruption. In endotoxemic animals, the authors showed that targeted suppression of TRPM7 through suppression/pharmacologic inhibition resulted in reduced renal vascular hyperpermeability, prevented kidney dysfunction, and improved survival. This work suggests TRPM7 as a novel molecular target in managing sepsis and resulting renal dysfunction in critically ill patients for whom these disorders are a common cause of death.

nature.com/pathology

c-Jun overexpression increases potency CAR T cells

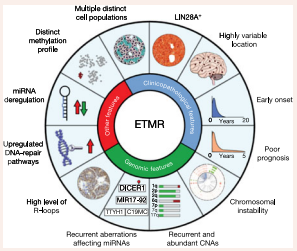
Chimeric antigen receptor (CAR) T cells have been shown to have anti-tumor effects with T-cell exhaustion playing an important role in decreased efficacy. Lynn et al. used a model system with tonically signaling CAR to simulate exhaustion and revealed several features of exhaustion, including increased chromatin accessibility of AP-1 transcription factor motifs. The group engineered CAR T cells to overexpress canonical AP-1 factor c-Jun and showed that the cells had enhanced expansion potential, increased functional capacity, diminished terminal differentiation, and improved anti-tumor potency in multiple mouse models in vivo. The authors propose that c-Jun overexpression may directly enhance c-Jun-mediated transcriptional activation of genes such as *IL2* and/or indirectly by disrupting or displacing AP-1i. Regardless, c-Jun appears to be a key feature in resisting exhaustion and increasing potency of CAR-T therapeutics across the class.



Nature 2019;576:293–300; https://doi.org/10.1038/s41586-019-1805-z

Characterizing ETMR to identify potential therapeutics

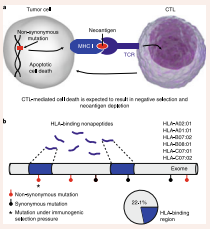
To investigate the genomic and molecular landscape of embryonal tumors with multilayered rosettes (ETMRs), Lambo et al. collected 193 primary and 23 matched relapsed samples. They investigated the driver microRNA cluster on chromosome 19 (C19MC), which is fused to *TTYH1* and often amplified. C19MC was not amplified when there were germline mutations in *DICER1* or other microRNA-related aberrations. Whole-genome sequencing revealed widespread occurrence of R-loop structures, causing genomic instability that could be related back to loss of DICER1 function. Topotecan alone was effective with half-maximum inhibitory concentration values of around 5 nM. The PARP inhibitors tested were less effective individually but when used together with topotecan they acted synergistically and led to a larger decrease in viability than monotherapy with any of the drugs. Using topoisomerase and PARP inhibitors, the authors propose, could target the R-loops and potentially provide a more targeted and more effective therapy for these patients.



Nature 2019;576:274–280; https://doi.org/10.1038/s41586-019-1815-x

Neoantigen depletion signals potentially inhibited by immune evasion

Van den Eynden et al. sought to investigate neoantigen depletion signals in the genome of untreated cancers, seeing these as a feature of somatic mutation accumulation. They used the human leukocyte antigen (HLA) family to demonstrate that signals of neoantigen depletion detected using HLA affinity predictions are, overall, weak to absent in the untreated cancer genome. HLA affinity predictions were used to annotate the human genome for its translatability to HLA binding peptides. The authors concluded that either only a very small fraction of predicted neoantigenic sites are immunogenic or the lack of negative selection signals suggests that developing tumors possess or evolve efficient immune evasion mechanisms (for example, HLA loss or programmed cell death ligand 1 amplification). This leaves room for further study of data sets including patients who have undergone immune-checkpoint therapy. Improved algorithms for predicting productive neoantigens are needed to improve our understanding of immunotherapy.



Nature Genetics 2019;51:1741–1748; https://doi.org/10.1038/s41588-019-0532-6