Modern Pathology (2015) 28, 746–747
© 2015 USCAP, Inc All rights reserved 0023-6837/15 $32.00

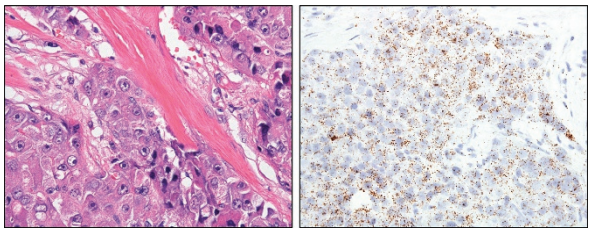
INSIDE THE USCAP JOURNALS

doi:10.1038/modpathol.2015.59

Modern Pathology

DNAJB1-PRKACA in fibrolamellar carcinoma

See page 822

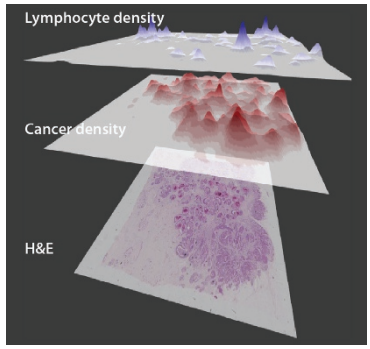


Recurrent gene fusions are being demonstrated in an increasing range of carcinomas. Predominantly affecting younger patients without underlying cirrhosis, fibrolamellar carcinoma is a distinct subtype of hepatocellular carcinoma that harbors a recurrent *DNAJB1-PRKACA* gene fusion. Graham and colleagues examined the specificity of this fusion within formalin-fixed paraffin embedded hepatocellular carcinoma cases using reverse transcriptase–polymerase chain reaction (RT-PCR) for the fusion transcript and fluorescence *in situ* hybridization (FISH) probes for rearrangement of the *PRKACA* locus. A subset of cases was studied using RNA *in situ* hybridization assay to assess expression levels of both the chimeric transcript and wild-type *DNAJB1* and *PRKACA* transcripts. This fusion gene was present in virtually all of the 26 cases of fibrolamellar carcinomas, as detected using both *PRKACA* FISH (100%) and RT-PCR (92%). The was no evidence of *DNAJB1-PRKACA* in conventional hepatocellular carcinomas, scirrhous hepatocellular carcinomas, cholangiocarcinomas, hepatic adenomas, or hepatoblastomas. The work confirms the specificity of the *DNAJB-PRKACA* fusion for fibrolamellar carcinomas and demonstrates the clinical applicability of multiple detection methods.

Immune infiltrate patterns in estrogen-negative breast cancer

See page 766

Assessment of tumor-infiltrating lymphocytes is increasingly emphasized as immune-modulating therapies are used in an expanding range of tumor types. Nawaz et al examined estrogen receptor–negative breast cancer, in which tumor-infiltrating lymphocytes confer a favorable prognosis. They applied automated histologic image analysis to hematoxylin and eosin slides and processed them with spatial statistical methods derived from ecology studies to rigorously quantify spatial heterogeneity. Using discovery and validation sets,

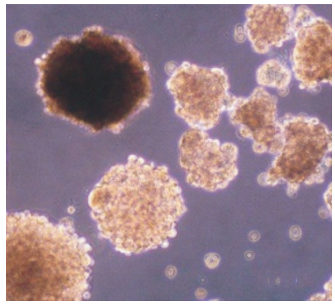


the authors demonstrated that colocalization of cancer cell and lymphocyte hotspots weighted by tumor areas was associated with improved outcomes in both univariate and multivariate analysis. Interestingly, application of this methodology to immune cell–rich tumors enabled further stratification. This study presents a novel technique for assessing not only the quantity of lymphocytes but also their spatial distribution in a formal fashion that can offer value and could be applied to a broader array of tumor types.

Laboratory Investigation

Phenotypic diversity of patient-derived melanoma stem cells

See page 672

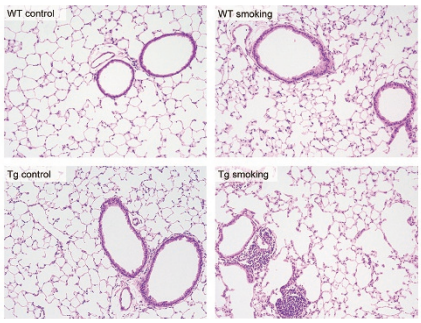


Sztiller-Sikorska and colleagues used melanospheres maintained in stem cell media to model the cellular diversity seen in melanoma tumors. In particular, cells with stem-like properties were maintained within melanospheres. Not all of the nodular melanoma patient–derived samples could produce melanospheres; instead, some produced cell aggregates and anchorage-independent single-cell cultures. In a comparison of melanospheres with other populations, the former showed increased expression of MITF. Interestingly, hypoxia-like conditions promoted melanosphere formation with enhanced MITF expression and melanocytic pigmentation, which was probably linked to the increased MITF. Over the two years of continuous

culturing, melanospheres progressively transitioned to cell aggregates, with significant loss of cellular heterogeneity. Given these data, consideration should be given to using melanospheres in pharmaceutical response studies to reflect the diversity of melanoma in patients. Although patient stroma is not accounted for, this approach may provide a better model of human melanoma.

Emphysema linked to proteasome activity

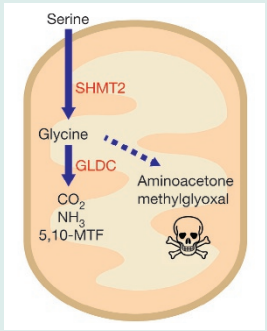
See page 625



Chronic obstructive pulmonary disease usually affects the elderly and results in progressive destruction of lung parenchyma and chronic airway inflammation. Its pathogenesis remains obscure; however, recent studies suggest that oxidative stress in alveolar cells may lead to apoptosis and emphysematous lung destruction. The proteasome is an enzymatic complex that proteolyzes improperly folded and modified proteins generated by oxidative and other stressors. It plays a key regulatory role in many physiologic processes, including cell proliferation, apoptosis, and immune reactions. Unfortunately, the proteasome's activity of declines with age, and it has been implicated in several age-related pathologies. Yamada *et al* investigated this decline in chronic obstructive pulmonary disease using a transgenic mouse that had specifically decreased proteosomal capacity and was exposed to cigarette smoke extract. Their model indicates that this combination accelerates the progression of emphysema through increased apoptotic cell death in the alveolar walls.

nature.com/pathology

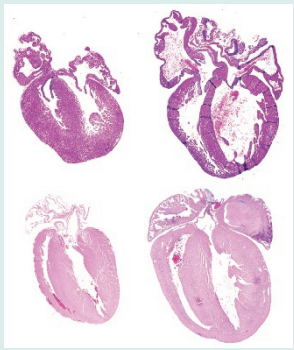
Survival of glioma cells in an ischemic environment



In a study published in *Nature*, Kim and colleagues examined how glioma cells survive and thrive in the poorly vascularized and oxygen-deprived tumor microenvironment. This has been believed to be accomplished, in general, by alterations of cell metabolism that promote cell survival, but the precise mechanisms are not known. The authors identify mitochondrial serine hydroxymethyltransferase (SHMT2) and glycine decarboxylase (GLDC) as being highly expressed in the pseudopalisading cells that surround necrotic foci in gliomas. SHMT2 activity inhibits pyruvate kinase (PKM2) activity, thereby greatly reducing oxygen consumption and conferring a strong survival advantage on these cells. Inhibition of GLDC impairs the glioma cells with elevated SHMT2 as excess glycine is shunted to aminoacetone and methylglyoxal, which are toxic to the cell. Thus, although SHMT2 allows glioma cells to adapt to a low-oxygen environment, it also appears to render them sensitive to inhibition of glycine cleavage. This suggests a novel therapeutic option.

Nature 2015;520:363–367; doi:10.1038/nature14363

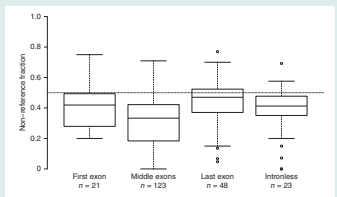
ERBB2 can help heal an ailing heart



The murine neonatal heart can regenerate in response to injury through cardiomyocyte proliferation, although this capacity markedly diminishes after the first week of postnatal life. Neuregulin-1 administration can promote cardiac regeneration, but it requires ERBB2 as a coreceptor. As reported in *Nature Cell Biology*, D'Uva and colleagues used a cardiomyocyte-specific *Erbb2* knockout to show that *Erbb2* is required for embryonic cardiomyocyte proliferation. Constitutively active ERBB2 expression in cardiomyocytes resulted in cardiomegaly due to extensive cardiomyocyte hypertrophy mediated by ERK, AKT, and GSK3β/β-catenin signaling pathways. When constitutively active ERBB2 was transiently induced in cardiomyocytes in an adult mouse model of myocardial infarction, cardiomyocytes were able to dedifferentiate, proliferate, redifferentiate, and regenerate functional cardiac tissue. ERBB2 thus appears to be necessary for cardiomyocyte proliferation, and manipulation of this pathway could have important therapeutic effects.

Nature Cell Biology, published online 6 April 2015; doi:10.1038/ncb3149

Homozygous loss-of-function mutations in humans



In *Nature Genetics*, Sulem *et al* describe their work with whole sequenced genomes of 2,636 Icelanders to catalog autosomal genes that were completely knocked out by rare loss-of-function mutations. The whole-genome results were used to identify the same events in a population of more than 100,000 chip-genotyped Icelanders. Approximately 6,800 autosomal loss-of-function single-nucleotide polymorphisms and insertions/deletions were identified in nearly 5,000 genes. Of genotyped Icelanders, 7.7% were homozygous or compound heterozygous in rarely mutated genes; there were complete knockouts in about 1,200 genes. The historical relative isolation of the population studied could partially account for these results. Genes highly expressed in brain were less commonly completely deleted than other genes. In addition, homozygous offspring of heterozygous parents were less frequently identified than expected, suggesting deleterious effects. These studies allow for linkage of homozygous losses to phenotypic traits and insights into genetic redundancy in humans

Nature Genetics 2015; 47:448–452; doi:10.1038/ng.3243