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MODERN PATHOLOGY

ALDH1 expression means better prognosis for melanoma

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Taylor *et al* sought to investigate aldehyde dehydrogenase 1 (ALDH1) expression as a biomarker in melanoma. ALDH1 is thought to be a biomarker of cancer stem cells in some human cancers. In tissue microarray studies of 68 melanoma patients, a low ALDH1 score was associated with a 3.7-fold increase in risk for melanoma-specific death within 10 years when compared with high ALDH1 levels ($p = 0.017$). Although ALDH1 expression has been correlated with poor patient outcome in some human cancers, in melanoma and other cancers higher expression has a favorable effect on patient survival. With ALDH1 shown to be a marker for tumor cell proliferation, survival, and resistance to chemotherapeutic agents, small molecules have been designed to inhibit its function. Given that the effects of both the protein and its inhibition are tumor type-specific, work needs to be done to develop ALDH1 as a therapeutic target in specific tumors.

HHV8-related lymphoid proliferations

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Seeking a better understanding of human herpesvirus 8 (HHV8)-associated lymphoid proliferations, Gonzalez-Farre *et al* reviewed 66 biopsy specimens from 61 patients with HHV8 infection. They identified 13 (20%) cases of HHV8-related

reactive lymphoid hyperplasia, 2 (3%) cases of HHV8 plasmablastic proliferation of the splenic red pulp, 28 (42%) cases of multicentric Castleman disease, 6 (9%) cases of germinotropic lymphoproliferative disorder, and 17 (26%) HHV8-related lymphomas. Of the 61 patients, 77% were also HIV-positive. The spectrum of disorders associated with HHV8 infection was wider than previously recognized. Of the 50 cases with HIV-associated reactive lymphadenitis, 26% showed HHV8-positive cells. HHV8-positive endothelial cells were seen in 5 cases, and 4 showed overt Kaposi sarcoma in the same lymph node. Epstein-Barr virus-positive lymphocytes were seen in 10 of the 11 cases, but their distribution differed from that of the HHV8-positive cells. The authors advocate routine HHV8 testing in all cases of lymphoid proliferation in immunosuppressed patients, particularly those who are HIV-positive. More outcome studies are needed.

LABORATORY INVESTIGATION

TGF- β induced fibrosis in scleroderma

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In scleroderma, both cutaneous and internal organ fibrosis are seen, with extensive collagen deposition within the extracellular matrix. Latent transforming growth factor- β (TGF- β) binding protein (LTBP-4) is known to activate TGF- β bioavailability and SMAD3 phosphorylation in lung fibroblasts, but a similar role for LTBP-4 has not been demonstrated in the dermal fibrosis characteristic of scleroderma. In a quantitative analysis, Lu *et al* found that LTBP-4 expression in scleroderma patients was enhanced in both skin sections and plasma. TGF- β expression was also elevated. When LTBP-4 was knocked down in skin fibroblasts the expression of collagen was also reduced, and

the group sought to explore the underlying relationships. The finding that SMAD2 and SMAD3 phosphorylation was inhibited in the skin fibroblasts with LTBP-4 knockdown indicated that inhibition of TGF- β /SMAD pathway may alleviate skin fibrosis.

Islet homeostasis and diabetes progression

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In type 1 diabetes, an autoimmune reaction destroys insulin-producing β -cells, resulting in unrestrained glucagon expression by α -cells. The identification of islet homeostasis protein (IHoP) led to an exploration of additional triggers for type 1 diabetes. Expression patterns for glucagon and IHoP were shown to be the same and overexpressed in diabetic islet α -cells. When IHoP expression was knocked down with small interfering RNA (siRNA), expression of glucagon was decreased. Oh and colleagues investigated not only the ways in which IHoP expression could prevent hyperglycemia using siRNA but also the potential use of IHoP expression as a biomarker for detecting type 1 diabetes in patients, an exciting possibility. Using IHoP-siRNA in nonobese diabetic mice islets, they demonstrated that islet regeneration is possible. This indicates that developing ways to reduce IHoP expression in human diabetic patients could reverse effects of islet damage and restore the prediabetic phenotype.

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Importance of intragenic DNA methylation

DNA methylation of CpG dinucleotide-rich areas within gene promoter regions leads to gene silencing and is a critical regulatory process in both healthy and diseased cells. However, the effects of DNA methylation within the body of the gene are not understood. Using mouse embryonic stem cells, Neri *et al* found that Dnmt3b-dependent intragenic DNA methylation protects the gene body from spurious RNA polymerase II entry and cryptic transcription initiation. After determining that Dnmt3b loss reduced gene-body DNA methylation, the group assessed the spurious transcripts that follow cross-talk between H3K36me6 and DNA methylation. They found that Dnmt3b was required for transcription-mediated fidelity and then that H3K36me3-dependent maintenance of transcription initiation fidelity was facilitated by Dnmt2b methylation. Intragenic DNA methylation, away from the promoter where this activity is best characterized, is thus an important factor to consider in gene expression studies and may play a role in cancer and other diseases.

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Using CRISPR/Cas9 to enhance immunotherapy

Chimeric antigen receptors (CARs) are synthetically produced receptors that can redirect and reprogram T cells to attack tumors with increasing success in multiple cancer types. Eyquem *et al* sought to generate uniform expression

of a CD19-specific CAR fused to the T-cell receptor (TCR) α constant (TRAC) and enhance T-cell potency by preventing T-cell exhaustion. Using the endogenous TRAC promoter, they were able to surpass other locus/promoter combinations in their *in vivo* assays. The group further demonstrate that targeting the CAR to the TRAC locus averts tonic CAR signaling and establishes effective internalization and re-expression of the CAR following single or repeated exposure to antigen, delaying effector T-cell differentiation and exhaustion. These findings reveal facets of CAR immunobiology and underscore the potential of CRISPR/Cas9 genome editing to advance immunotherapies. The authors suggest that targeting CARs to a TCR locus may even provide a safer therapeutic T cell, minimizing risks of insertional oncogenesis and TCR-induced autoimmunity and alloreactivity.

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CD109–Jak–Stat3 axis promotes lung metastasis

Having developed molecular barcodes for cells within a mouse tumor xenograft model, Chuang *et al* were able to grow and then use flow cytometry to distinguish between the primary nonmetastatic cells and those that had seeded metastatic sites of tumor burden. Microarray analysis of the separated groups of cells enabled the authors to distinguish expression patterns between cell types and even different stages in tumor development and metastatic progression. CD109 emerged as a driver of metastatic ability of the cancer cells *in vivo*, and systematic knockdown of candidate genes showed that CD109 was regulating Stat3 activity and driving both the malignant phenotype and metastatic ability. Pharmacological inhibition of Jak–Stat signaling inhibited the metastatic ability of lung adenocarcinoma cells, leading the group to conclude that Jak kinases are required for CD109-induced Stat3 activation and metastatic potential of lung adenocarcinoma. The findings indicate that Jak family kinases are a target for therapeutic development.

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Emma Judson contributed to these reviews.