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Role of hemidesmosomes in invasive squamous cell carcinoma

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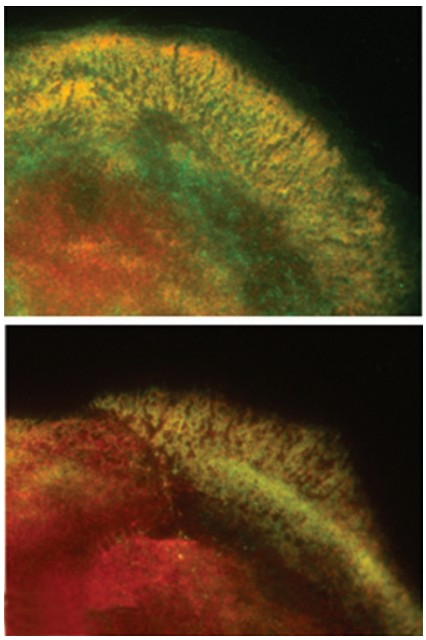

Stratified squamous epithelia serve important barrier functions in squamous mucosa and skin. To ensure integrity of the barrier, they are firmly anchored to the basal lamina by hemidesmosomes (HDs). Squamous cell carcinomas (SCCs) are invasive and aggressive cancers that arise mostly from stratified squamous epithelia. During invasion, neoplastic squamous cells invade through the basal lamina into adjacent soft tissue and blood vessels. This process is helped by the destruction of HDs, which might otherwise oppose invasion.

HDs are multiprotein assemblies containing $\alpha 6\beta 4$ integrin, a protein with a central role in their maintenance. $\alpha 6\beta 4$ integrin connects to laminin on the basal lamina and facilitates assembly of other HD components that eventually bind to cytokeratins. Phosphorylation of critical serine residues is known to alter $\beta 4$ integrin function. On the basis of these data, Kashyap *et al* hypothesized that $\beta 4$ integrin phosphorylation might alter HD stability during SCC invasion.

Using phospho-specific antibodies, the authors demonstrated that $\beta 4$ integrin phosphorylation at serine 1356 correlated with SCC invasion in tissue sections. The pattern of phosphorylation was discontinuous and more prominent at the tumor–stroma interface, suggesting a causal relationship between $\beta 4$ phosphorylation and invasion. They also showed that $\beta 4$ phosphorylation was dependent on the epidermal growth factor/protein kinase C (EGF/PKC) pathway, although the EGF receptor appeared to have intrinsic activity that was not further stimulated by exogenous EGF. Finally, their findings suggest that, although HD destabilization is important for SCC invasion, it does not play an important role in SCC migration. In summary, this study demonstrates that HD destabilization through EGF/PKC signaling plays a critical role in SCC invasion.

Disease-defining translocation in nodular fasciitis

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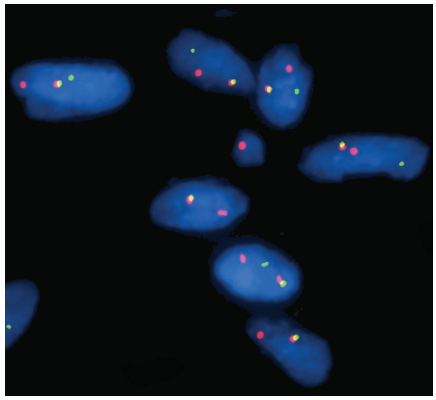

Nodular fasciitis (NF) is a common fibroblastic tumor that occurs predominantly in the extremities of adolescents and young adults. Although lesions grow rapidly and contain numerous mitotic figures, they regress if they are left untreated. This has led to vigorous debate about whether or not NF is a neoplasm.

While studying the expression patterns of *USP6* (ubiquitin-specific protease 6), which encodes a de-ubiquitinating enzyme that is involved in a wide array of cellular processes and is expressed almost exclusively in testes, Erickson-Johnson *et al* found that *USP6* was strongly expressed in NF. They showed that *USP6* was fused to *MYH9* (myosin heavy-chain 9), which encodes a member of the nonmuscle myosin class II family and is strongly expressed in fibroblasts. The fusions were predicted to express virtually full-length *USP6* from the noncoding exon 1 of *MYH9*. Thus, *USP6* is overexpressed by a promoter-swapping mechanism whereby it is expressed via the *MYH9* promoter, which in turn is strongly expressed in fibroblasts. *USP6* and *MYH9* gene rearrangements were found exclusively in NF; thus, the *MYH9-USP6* gene fusion is disease defining for NF. When the authors injected a murine pre-osteoblastic cell line expressing *USP6* subcutaneously into nude mice, tumors with the histologic features of NF grew but regressed within 2 to 3 weeks. These results strongly support that NF is a neoplasm—although one with a limited life span, leading the authors to suggest that NF represents the first reported example of what they call "limited neoplasia."

miRNA-148a suppresses tumor formation by targeting *CDC25B*

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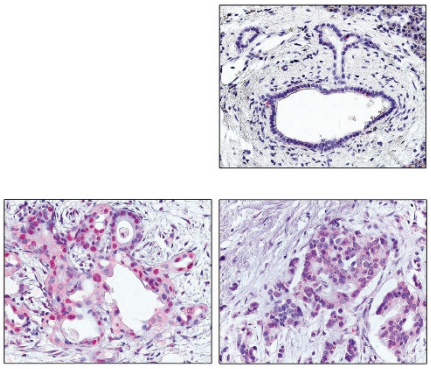
MicroRNAs (miRNAs), which exert their action by negatively regulating RNAs post-transcriptionally, are emerging as important oncogenes and tumor suppressors. Cancer-specific miRNAs are known as oncomiRs. *miR-148a* is downregulated in several types of solid cancers, suggesting that it is a tumor suppressor. To understand how it functions as a tumor suppressor, Liffers *et al* used an *in silico* approach to identify

miR-148a targets that might be important in cancer initiation and progression in pancreatic adenocarcinoma.



There are several known targets of *miR-148a*, but the authors' analysis suggested that *CDC25B* is an additional target because it contains a putative *miR-148a* binding site at the end of its 3′*UTR*. Reporter studies and overexpression studies showed that *miR-148a* reduces CDC25B levels, confirming that it is a target. CDC25 proteins are dual-specificity phosphatases that positively regulate cell cycle progression. CDC25B activates the CDK1/cyclin B complex at the G2/M checkpoint to initiate mitosis. Functional analysis showed that forced *miR-148a* expresson in a pancreatic cancer cell line reduced cell growth and proliferation, which is in keeping with the hypothesis that it acts by suppressing CDC25B. Furthermore, *miR-148a* suppressed expression of *CDC25B* in several pancreatic cancer cell lines. Evaluation of human tissues revealed that *miR-148a* levels were high in normal pancreatic epithelium and low in pancreatic adenocarcinoma precursors (PanINs) and pancreatic adenocarcinoma. Together these data led the authors to propose a model whereby repression of *miR-148a* by promoter hypermethylation is an early event in pancreatic adenocarcinoma carcinogenesis. The resultant increase in CDC25 facilitates increased genomic instability, resulting in the accumulation of oncogenic mutations that lead to tumor progression.

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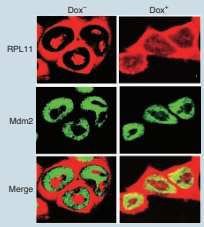
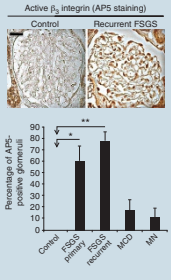
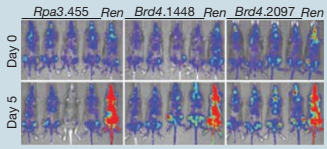


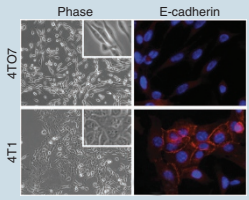
Context is important for PICT1 function in cancer PICT1 has been thought to act as a tumor suppressor because it stabilizes PTEN and because low PICT1 expression is associated with tumor progression in some cancers. However, loss of heterozygosity at chromosome 19q13, the location of *PICT1*, is associated with good prognosis in oligodendroglial tumors. Sasaki *et al*, as recently reported in *Nature Medicine*, have resolved this apparent paradox. They demonstrated that PICT1 binds RP111, a nucleolar protein, which prevents it from binding MDM2, an E3 ubiquitin ligase that promotes p53 degradation. Thus, loss of PICT1 results in accumulation of p53. Although this does not affect cancers with inactivating p53 mutations, the response to increased p53 by cancers with functional p53 is decreased growth and increased apoptosis. It is therefore not surprising that loss of PICT1 is associated with a better prognosis in oligodendrogliomas, a tumor type characterized by a high percentage of cases with wild-type p53.
Nature Medicine 2011;17:944–951; doi:10.1038/nm.2392



Cause of focal segmental glomerulosclerosis is identified Focal segmental glomerulosclerosis (FSGS) is a major cause of end-stage renal disease. On the basis of clinical observations, it has been hypothesized that a circulating factor within the serum known as FSGS permeability factor causes FSGS. In a recent article in *Nature Medicine*, Wei *et al* reveal the identity of FSGS permeability factor as serum-soluble urokinase receptor (suPAR). They found that suPAR levels correlated specifically with FSGS and even predicted recurrence in recipient transplant kidneys. Glomerular damage was caused by podocyte β_3 integrin activation by suPAR. The authors showed that interventions that lowered suPAR or interfered with suPAR-β_3 integrin interaction prevented FSGS. These results lay the groundwork for improved therapies for this serious renal disease.
Nature Medicine 2011;17:952–960; doi:10.1038/nm.2411



Brd4 controls oncogenesis in acute myeloid leukemia Epigenetic changes collaborate with a variety of oncogenic fusions to alter common core cellular processes that maintain a leukemic stem cell state in acute myelogenous leukemia (AML). As described in a recent letter in *Nature*, Zuber and colleagues used a customized RNA interference screen to identify epigenetic regulators that contribute to oncogenesis in AML. They identified Brd4, a member of the BET family of bromodomain-containing proteins that bind to acetylated histones to influence transcription, as important for cell survival. Targeting Brd4, either pharmacologically or by short hairpin RNA, caused terminal myeloid differentiation and elimination of AML stem cells through inhibition of Myc. The authors also demonstrated that Brd4 appears to influence Myc primarily in oncogenesis, suggesting that inhibition of Brd4 may be a good strategy to control oncogenic Myc.
Nature, published online 3 August 2011; doi:10.1038/nature10334



miR-200s promote metastatic colonization Functional studies of miR-200s have shown conflicting results with respect to whether these microRNAs promote or hinder metastasis. In a recent article in *Nature Medicine*, Korpal *et al* show that they do both. The authors argue that in the early stage of metastasis, when cells invade lymphatics and blood vessels, an epithelial-to-mesenchymal cancer cell transition is desirable, whereas in the later stage of colonization of distant sites, a mesenchymal-to-epithelial (MET) cancer cell transition is advantageous. Because miR-200s facilitate MET, they inhibit the early stage of metastasis but facilitate the later stage of colonization of distant sites. Furthermore, the investigators demonstrated that miR-200 expression induces secretion of proteins that enhance metastatic colonization by influencing the microenvironment.
Nature Medicine, published online 7 August 2011; doi:10.1038/nm.2401