knowledge increases our understanding of how TrkB could function in aggressive human cancers, and provides important insight into the functional relationship of two key transcriptional regulators of metastasis.

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Myc and Mnt in lymphomagenesis

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The aim of this work was to investigate whether Mnt is a "master" controller of Myc complexes. Myc plays a central role in controlling cell growth, proliferation, transformation and apoptosis is deregulated in over 70% of human tumors. Mnt is thought to antagonize Myc by competitively binding to its binding partner Max and repressing gene expression. Consistent with this view, knockdown of Mnt has been shown to mimic Myc over-expression (1) and conditional Mnt deletion in mice results in mammary adenocarcinoma and T-cell lymphoma (2,3).

Recent work from our laboratory using transgenic mice emphasizes the importance of Myc levels in the development of haemopoietic malignancy (4,5). We are currently evaluating the impact of loss of Mnt in these VavP-myc10 transgenic mice. Mice bearing one copy of the VavP-myc10 transgene succumb to lymphomas of monocytic origin with a median of 41 weeks (5), while those bred to have two copies develop lethal early-onset T-cell lymphomas (median 13 weeks) (5). As the level of Myc determines both tumor kinetics and phenotype, we hypothesised that a decrease in Mnt would increase the functional level of Myc. In VavP-myc10 mice we expected this to result in acceleration of tumourigenesis and a switch of phenotype to T-cell lymphomas in mice carrying only one copy of the VavP-myc10 transgene.

Surprisingly, we found that heterozygous deletion of Mnt did not advance the onset of tumourigenesis or promote T-cell lymphomagenesis in VavP-myc10 mice. As Mnt null mice are not viable, we have now crossed Vav-Cre deleter mice with mice carrying floxed Mnt alleles to inactivate Mnt in all haemopoietic cells. These mice are viable and will be used to investigate if complete loss of Mnt disturbs haemopoiesis and results in lymphomagenesis in a manner similar to Myc over-expresson.

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A novel gene downstream of Pax2 is overexpressed in Wilms' tumors and encodes for a Calcineurin A binding protein

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Background: Wilms' tumor (WT) accounts for approximately 85% of childhood kidney cancer and occurs at a frequency of 1 in 10,000 live births. WT is a classical cancer type arising from abnormal differentiation of kidney progenitor cells. Pax2 (Paired-Box) is recognized as a critical regulator of kidney development. Pax2 expression normally attenuates as the kidney matures; however, abnormally high PAX2 levels have been observed in both WT and renal cell carcinoma. PAX2 expression in kidney cancer cells correlates with proliferation and increased invasive phenotype. Based on the above evidence, we believe that the misexpression of PAX2 and its target genes play an important role in tumor initiation and/or progression.

Methods and Results: To test this hypothesis, we screened for target genes of Pax2 by cDNA microarray in the embryonic kidney. From this, we identified a novel gene, called CnABP for Calcineurin A Binding Partner, under Pax2 regulation. In situ hybridization indicates that CnABP coexpresses with Pax2 in the condensing mesenchyme, progenitor cells of Wilms' tumor. Expression analysis by quantitative PCR indicates that CnABP is overexpressed in more than 70% of Wilms' tumors. Interestingly, in the proportion of tumors with upregulated Pax2 expression, more than 80% also overexpress CnABP. CnABP is a highly conserved protein containing a N-myristoylation signal and a Calcineurin binding motif. Functional analysis indicates that CnABP is a membrane-anchored protein that primarily promotes cell migration. Yeast-two-hybrid and immuno-precipitation identify an interaction between CnABP and Calcineurin A, the catalytic subunit of a calcium-responsive serine/threonine phosphatase. Importantly, we showed that CnABP modulates phosphatase activities of Calcineurin.

Conclusions: Recently, components of the Calcineurin complex have been implicated as signature genes for recurrent Wilms' tumor. This is in line with the evidence we presented, as CnABP is upregulated in Wilms' tumors and is shown to promote migration. Together these data identify a new promigratory protein regulated by Pax2 that potentially play a role in tumor progression.

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Tissue-specific ablation of Prkar1a causes schwannomas by suppressing neurofibromatosis protein production

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Background: Signaling events leading to Schwann cell tumor initiation have been extensively characterized, owing to their association with the well-studied inherited tumor syndromes Neurofibromatosis (NF) Types 1 and 2. Similar tumors are also observed in patients with the endocrine neoplasia syndrome, Carney Complex (CNC), which results from inactivating mutations in PRKAR1A, the gene encoding the Type 1A regulatory subunit of the cAMP-dependent protein kinase (PKA). Loss of PRKAR1A leads to enhanced PKA activity, although the pathways leading to tumorigenesis are not well characterized. Materials and methods: We previously reported that Prkar1a$^{+/-}$ mice are tumor prone, and approximately 33% of these mice develop schwannomas. Similar tumors are observed in a limited neural crest knock-out of Prkar1a (TEC3KO) with nearly 80% penetrance by 10 months. These heterogeneous neoplasms occurred either uni- or bilaterally, and were clinically characterized as genetically engineered mouse (GEM) schwannomas, grades II and III. The TEC3KO tumors were further studied for the molecular mechanisms by which PKA dysregulation may affect NF signaling. Results: At the molecular level, analysis of the TEC3KO tumors revealed almost a complete loss of both NF proteins, whereas transcript levels were increased; indicating post-transcriptional regulation. Although Erk and Akt signaling are typically increased in NF-associated tumors, we observed no activation of either of these pathways in our tumors. Furthermore, the small G-proteins Ras, Rac1, and RhoA are all known to be involved with NF signaling. In TEC3KO tumors, all three molecules showed modest increases in total protein, but only Rac1 showed significant activation. Conclusions: These data suggest that dysregulated PKA activation causes tumorigenesis via pathways that overlap but are distinct from those described in NF tumorigenesis.

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Triterpenoids affect angiogenesis and prevent neoplastic progression

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INTRODUCTION: Angiogenesis is the base for solid tumor growth and dissemination; recently anti-angiogenic drugs have begun to show promise in clinical trials. We propose to identify molecules and pathways involved in cancer progression in order to prevent neoplastic development and metastatic dissemination. Chemoprevention focuses on the primary or secondary prevention of cancer using natural or synthetic agents usually showing mild or no collateral effects.

MATERIALS: We have recently assessed the activity of novel compounds, CDDO-Me and CDDO-Im, derived from the olanoleic acid triterpenoid, that have shown a potent antiangiogenic activity at really low dosages. In vivo we performed matrigel sponge assay; on day +4 day from matrigel injection, CDDO-treated and CTRL nu/nu CD1 mice were sacrificed to measure Hb content in matrigel sponges. Then we tested CDDO analogues efficacy in Kaposi's sarcoma xenograft; after KS-Imm cells injection in C57BL mice, we administered CDDO or vehicle and monitored tumor growth. On day of sacrifice tumors were isolated and processed for morphological and IHC analysis.In vitro we evaluated HUVECs ability to organize in capillary-like structures in matrigel, in presence of CDDO analogues or vehicle. Then we treated HUVECs and quantified proliferation. By immunofluorescence we investigated whether these compounds affect NF-kB pathway in HUVECs.