p38 and STAT3 activation that is NFκB-independent. We demonstrate further that Src activation contributes to the expression of the transcriptional repressor, Id2 (Inhibitor of differentiation 2), expressed in pancreatic (and some other) tumor cells but not in normal adult cells. Expression of Id-2 is regulated transcriptionally by Hif-1α, and, in turn, Id-2 regulates Hif-1α stability, thereby contributing to increased expression of VEGF in tumor cells. These results suggest that Src activation deregulates multiple pro-angiogenic programs that may provide markers as well as targets for novel therapies.

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S3. AP-1-DEPENDENT GENE EXPRESSION DURING SKIN TUMOURIGENESIS

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The transcription factor AP-1, which is composed of members of the Fos, Jun and ATF protein families participates in physiological and pathophysiological processes due to its central role as a cellular switch of genetic programs in response to extracellular signals. The distinct expression pattern of AP-1 subunits in the skin, the loss of chemically induced carcinogenesis in AP-1 compromised mice, and the large number of putative AP-1 target genes in epidermal cells, indicate that AP-1 members play a pivotal role in epidermal organisation, skin homeostasis and tumourigenesis. To define AP-1-dependent genetic programs associated with distinct stages of tumourigenesis in vivo we have combined the well-established chemically induced mouse model of epithelial skin tumours and comprehensive expression profiling. A series of novel tumour-associated genes could be identified including previously unrecognized molecules involved in protein trafficking and novel serine and aspartic proteases, which are expressed depending on the differentiation and progression state of the tumours. Moreover, four members of the S100 family of Ca^{2+} binding proteins, S100A3, A6 and A8, A9 were identified, which are differentially expressed in murine and human epithelial tumours of the skin and other organs. These molecules are part of a novel signalling pathway controlling AP-1 and NFκB-dependent genetic programs, which are likely to play an important role in tumour formation, progression and metastasis.

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S4. ENZASTAURIN – FROM BENCH TO BEDSIDE, AND BACK

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Enzastaurin is an oral serine-threonine kinase inhibitor of the PI3K signaling pathway and PKCβ. In preclinical in vitro and in vivo tumor models, enzastaurin promotes apoptosis, inhibits tumor cell proliferation and blocks tumor-induced angiogenesis. Phase II studies showed encouraging efficacy in heavily pretreated patients with glioblastoma multiforme and diffuse large B cell lymphomas, respectively. Prospective randomized phase III trials are about to commence in these two tumor types. Phase II trials are in progress or development in a variety of cancers, including breast, ovarian, colon, prostate, non-small cell lung cancer, chronic lymphocytic leukemia and follicular lymphomas. The available safety data show good tolerance of enzastaurin when used as a single agent. Phase I studies in combination with various cancer agents, cytotoxic as well as biologically targeted, are in progress. Most enzastaurin trials include tumor tissue collection for correlative analysis of candidate biomarkers and clinical outcome. We hope this will allow selection of those cancer patients in the future who gain most benefit from enzastaurin treatment.

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S5. SURVIVING AND TRANSFORMING GROWTH FACTOR BETA (TGF-β) AS DRUG TARGETS IN CANCER

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The molecular heterogeneity of malignant cells and their interaction with the surrounding microenvironment is one of the most challenging aspects of drug development in oncology. Developing successful drug intervention strategies requires the identification of molecular targets that show high impact on either tumor cell growth or the supporting microenvironment. In recent years, several such targets have been proposed, including Survivin and TGF-β. Survivin is uniquely upregulated in most cancer cells, while in non-malignant cells it is generally not expressed. Thus, an inhibition of Survivin could lead to a selective treatment of malignant cells without affecting normal tissue cells. Because of its structure, selective small molecule inhibitors are difficult to identify.

In collaboration with Isis Pharmaceuticals (Carlsbad, CA, USA) Eli Lilly and Company (Indianapolis, IN, USA) (Lilly) developed a second generation antisense oligonucleotide (ASO) that is specific for the inhibition of Survivin in cells. This ASO against Survivin has been evaluated in various non-clinical in vitro and in vivo models confirming its specificity. Based on this information, a phase I clinical trial was started to evaluate its safety and pharmacokinetic profile in cancer patients. In contrast to a target in cancer cells, inhibiting TGF-β signaling is designed to modulate the microenvironment of cancer cells. Lilly developed various small molecule inhibitors for the TGF-β receptor type I (TGF-βRI) kinase. From this series of molecules, one inhibitor has been selected for clinical investigation. The compound LY2157299 has demonstrated anti-tumor activity in various non-clinical in vitro and in vivo models, supporting its evaluation in a phase I clinical trial of patients with cancer. In summary, Lilly has a comprehensive program to develop inhibitors of tumor cells and their supporting microenvironment, such as Survivin and TGF-β.

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