Role of p63 in Keratinocyte Differentiation and Proliferation
A Costanzo 1, B Marinari 1, M Koster 2, ML Giustizieri 1, C Ballaro 3, S Role of p63 in Keratinocyte Differentiation and Proliferation
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The p63 gene belongs to the p53 gene family of tumor suppressor genes and encodes for sequence specific transcription factors. The DNp63 protein, lacking the canonical transactivation domain, has been proposed to identify the epidermal stem cells and to regulate their survival and self renewal. In an attempt to identify new potential p63 targets, we have found that the epidermal morphogenesis modulator IKKa is tightly regulated at the transcriptional level by different isoforms of p63. We have observed that IKKa mRNA expression increases at the onset of the stratification program. The selective downregulation of DNp63 by siRNA in primary keratinocytes abolishes IKKa activation and the onset of terminal differentiation and increases keratinocyte proliferation rate. This is consistent with transcriptional assay data performed with an IKKa-promoter reporter gene showing a strong activation of IKKa transcription by DNp63 isoforms and a repressory activity of TAp63 isoforms. On the other hand, the downregulation of IKKa in primary keratinocytes hampers the ability of differentiating cells to exit the cell cycle inducing the formation of a K1 expressing proliferative layer that is reminiscent of the embryonic intermediate layer and of squamous cell carcinoma. Our results indicate IKKa as an important p63 target potentially involved in the control of epidermal stem cells proliferation in skin development and in cell transformation.

Molecular Pathogenesis of Basal Cell Carcinoma
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The hedgehog signalling pathway plays an important role in the embryonic development of various organ systems including the skin. Aberrant activation of hedgehog signalling by mutations in genes encoding important members of this pathway, such as the hedgehog receptor genes PTCH and SMOH, plays a crucial role in the pathogenesis of basal cell carcinomas, the most common human cancers. Germline mutations in the PTCH gene underlie the early and multifocal development of basal cell carcinomas in patients suffering from nevoid basal cell carcinoma syndrome. Somatic mutations in PTCH or SMOH as well as upregulation of different hedgehog target genes are found in the vast majority of sporadic basal cell carcinomas. In addition, about 50% of the cases carry mutations in the TP53 tumor suppressor gene. Recent progress in the understanding of the complex molecular pathogenesis of basal cell carcinoma, including data obtained from experimental studies on genetically modified mouse models, will be discussed.

Genes Involved in Polygenic Inheritance to Melanoma
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Germline mutations affecting two highly penetrant melanoma-predisposing genes, CDKN2A and CDK4, are associated with familial cutaneous melanoma, which accounts for 5-10% of all melanoma cases. In addition, there is increasing evidence for a polygenic inheritance of the predisposition to melanoma, and variant alleles associated with melanoma risk have been identified at several gene loci, such as genes involved in DNA repair (XRCC3), reactive oxygen detoxification (Glutathione S-transferases M1 and T1) and pigmentation (melanocortin 1 receptor, MC1R). In particular, specific loss-of-function MC1R variants are believed to be low penetrance melanoma-predisposing mutation{s} (Hayward, 2003) that have also been shown to modulate the penetrance of CDKN2A mutations in melanoma families. Because of the important role of melanin in protecting the skin against UV radiation, genes that control melanocyte development or melanogenesis are attractive candidates, and these include the endothelin system, that plays a crucial role in melanocyte development, differentiation, and response to UV radiation. we recently showed in a case-control study that non-synonymous variants of the endothelin B receptor (EDNRB), a gene involved in melanocyte differentiation, were associated with melanoma risk, suggesting that a defect in EDNRB could favour melanoma development.

Viruses as Therapeutic Tools in CTCL
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Primary cutaneous T-cell lymphomas (CTCL) are a nice example how profound knowledge of the immune biology can be translated into well tolerated treatment approaches. We have purified the tumor cell populations in CTCL patients by the use of monoclonal antibodies directed against T-cell receptor variable region and studied the cytokine transcription profile and cytokine responses. The tumor cell populations preferentially secret T-helper 2 cytokines (IL-5, IL-10), the Interferon signaling pathway was found to be deficient. This Interferon resistance affects also the susceptibility for viral infections. Interferon sensitive viruses such as vesicular stomatitis virus selectively replicate in the tumor cell population in the presence of exogenous Interferon-alpha. Consequently, we have initiated a clinical trial using replicating measles virus in CTCL patients. In order to target the T-helper 2 neoplasms, we have also initiated a clinical trial using an adenoviral vector of the third generation expressing Interferon-gamma after demonstrating the expression of the human adeno- and coxsackie virus receptor in CTCL biopsies. Efficient expression of the adenoavirus encoded Interferon-gamma was detected after injection. Repetitive injections of the vector resulted in substantial regressions of injected and non-injected skin lesions in cutaneous T-cell but also in cutaneous B-cell lymphomas associated with an increase of reactive cytotoxic mononuclear cells. We are convinced that a detailed analysis of cancers will identify Achilles heels that can be targeted by specific molecular interventions. Cutaneous neoplasms are perfect prototype tumors since they can be easily reached for intralesional injection and repeated biopsies during therapeutic interventions.
Mechanisms of Melanoma Metastasis Formation

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Malignant melanoma is an aggressive malignant tumor and its high tendency to metastasize represents the major survival-limiting factor for patients with this disease. Previously, we reported that chemokine receptors are involved in site-specific metastasis of breast cancer. Here, we show that melanoma cells preferentially express two chemokine receptors, CXCR4 and CCR10. In melanoma, CXCR4 expression directly correlates with the invasive stage of the primary tumor, is induced by TGF-beta1 and shows enhancement at the invasive tumor front. Furthermore, growth factors produced within the local tumor microenvironment such as bFGF, EGF, and TGF-beta1, or the proinflammatory cytokines TNF-alpha and IL-1beta induce chemokine receptor expression on melanoma cells. In vivo, neutralization of CXCL12/CXCR4 interactions results in significant suppression of the development of lung metastases. Clinically, melanoma is characterized by a high frequency of skin metastases which correlates with the abundant expression of CCR10, a receptor binding to the skin-specific chemokine CCL27. Notably, cutaneous and subcutaneous melanoma metastases exhibit significantly increased levels of CCR10 suggesting the selection of CCR10-high expressing melanoma cells. In addition to the induction of migration and invasion, CCL27 also enhances melanoma cell proliferation in vitro and in vivo. Taken together, our findings strongly suggest that specific chemokine receptors play critical roles in tumor progression and metastasis of malignant melanoma.