proper MT dynamics, in particular mitosis, are affected by loss of VHL function. We found that VHL localizes to the mitotic spindle and functions to suppress spindle mis-orientation and to promote chromosomal stability by positively regulating Mad2 mitotic checkpoint protein expression. An association between VHL inactivation, reduced Mad2 levels and increased aneuploidy was also found in human renal cancer, implying that this newly identified functions of VHL in promoting proper spindle orientation and chromosomal stability likely contribute to tumour suppression (Thoma et al., in press).

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5 INVITED

Hypoxia-inducible factor 1 in cancer pathogenesis and therapy

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Hypoxia-inducible factor 1 (HIF-1) regulates the transcription of many genes involved in key aspects of cancer biology, including immortalization, maintenance of stem cell pools, cellular dedifferentiation, genetic instability, vascularization, metabolic reprogramming, autocrine growth factor signaling, invasion, metastasis, and treatment failure. HIF-1 is a heterodimeric protein composed of a constitutively expressed HIF-1β subunit and an O2-regulated HIF-1α subunit. In animal models, forced HIF-1α overexpression is associated with increased tumor growth, vascularization, and metastasis, whereas HIF-1 loss-of-function has the opposite effect. Immunohistochemical detection of increased HIF-1α protein levels in tumor biopsy sections, or microarray detection of increased HIF-1 target gene expression, is a negative prognostic factor in many types of human cancer. These findings have validated HIF-1 as a therapeutic target.

A cell-based screening assay for drugs that inhibit HIF-1-mediated transcription revealed that cardiac glycosides, such as digoxin, inhibited: synthesis of HIF-1α protein; expression of HIF-1 target genes that regulate angiogenesis (VEGF), glucose transport (GLUT1), and glycolysis (HK1, HK2); and the growth of human hepatoma, lymphoma, and prostate cancer xenografts. Anthracycline compounds, such as doxorubicin, did not affect the levels of HIF-1α but instead inhibited the binding of HIF-1 to hypoxia-response element sequences in target genes such as VEGF and PDK1. Daily low-dose doxorubicin administration rapidly arrested the growth of prostate cancer xenografts and blocked the intratumoral expression of HIF-1-regulated angiogenic cytokines (VEGF, stem cell factor, and stromal-derived factor 1), tumor-induced mobilization of angiogenic cells into peripheral blood, and tumor vascularization.

Taken together, the large body of clinical and experimental data regarding the role of HIF-1 in human cancer pathogenesis suggests that the addition of HIF-1 inhibitors to therapeutic regimens may improve outcome in patients whose tumor biopsy reveals high levels of HIF-1α in a tumor type in which such overexpression is associated with increased mortality (bladder, brain, breast, cervical, colorectal, endometrial, gastric, gastrointestinal stromal cell, non-small cell lung, oropharyngeal squamous cell, ovarian, and pancreatic cancer). In particular, digoxin and other cardiac glycosides have been used to safely and chronically treat patients with congestive heart failure and epidemiological studies have associated such treatment with reduced incidence of bladder and kidney, breast, and prostate cancer.

6 INVITED

Hypoxia signalling, metabolism and cancer

J. Pouyssegur[1], J. Chiche[1], R. LeFloch[1], K. Ilc[1], D. Roux[1], C. Brahimi-Horn[1], N. Mazure[1]. [1]*Centre Antoine Lacassagne, CNRS-UMR, Nice Cedex 2, France*

Without nutrient sensing and feedback from the tissue microenvironment, fast growing cells of the developing embryo and of expanding tumors would rapidly outstrip the supply of nutrients and die. Although cells sense and respond to variations in the concentration of key nutrients, oxygen sensing has emerged, early on in evolution, as a central control mechanism of energy metabolism and vasculogenesis. At the heart of this regulatory system is the Hypoxia-Inducible Factor, HIF, which controls, among other gene products, the expression of VEGF-A and Angiopoietin-2, two key angiogenic factors. This finding has placed the hypoxia-signaling pathway at the forefront of nutritional control. HIF can induce a vast array of gene products controlling glycolysis, intracellular pH (pHi), angiogenesis, cell migration and invasion, and so has become recognized as a strong promoter of tumor growth. The pro-invasion feature of HIF, measured by stimulation of Epithelial-Mesenchyme-Transition, could be seen as an integrated program 'designed' for migration-induced nutrient-search, as in microorganisms. It is therefore not surprising that HIF also promotes access to another source of nutrients by inducing macro-autophagy. In the context of this symposium, we will highlight some of the HIF-induced gene products that participate in tumor adaptation, resistance and progression in a nutrient-depleted and acidic microenvironment.

First we will demonstrate that the two HIF-induced 'BH3-only'-proteins (BNIP3, BNIP3L/NIX), in contrast to the current believe, do not trigger cell death but, by inducing macro-autophagy, stimulate tumor cell survival. We propose a model in which the low-affinity BH3-domains of hypoxia-induced BNIP3/BNIP3L have been 'designed' to induce autophagy. They can disrupt the Beclin1-Bcl2 and Beclin1-Bcl-XL complexes without inducing cell death.

Second, we will show how tumor cells by expressing two HIF-dependent membrane-bound carbonic anhydrases, CAIX and CAXII, acidify the extracellular milieu, and ensure a more alkaline intracellular pH favoring migration, survival and growth in a hostile acidic microenvironment. Inducible knock down of CAIX and CAXII by short hairpin interfering RNA is able to severely reduce growth of colon adeno-carcinoma spheroids and tumors in *nude* mice.

Third, HIF-induced glycolysis in most hypoxic tumor cells is essential to ensure maintenance of ATP levels for growth and cell survival. Two MonoCarboxylate Transporters MCT-1 and MCT-4, stabilized in the plasma membrane by the common chaperon basigin/CD147, play a key role in cancer metabolism. These transporters are critical for lactic acid export. Inactivation of MCT-1 the only form expressed in Ras-transformed fibroblasts abolishes tumor growth. We will show that the hypoxia-induced MCT-4 is critical for tumor resistance, survival and tumor growth in human epithelial tumors. Combined inactivation of both MCT-1 and MCT-4 is required to collapse tumor growth.

We propose that appropriate exploitation of these HIF-regulated proteins and new validated cancer targets, which control exacerbated tumor metabolism and intracellular pH, will be at the forefront of anti-cancer therapy.

Scientific Symposium (Mon, 21 Sep, 11:00−13:00)
Symptom clusters in cancer therapy

7 INVITED

What's new, what's best in symptom management?

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The majority of symptom management research in oncology has focused on an evaluation of single symptoms (e.g., fatigue, pain, nausea, vomiting). However, clinical experience suggests that oncology patients rarely present with a single symptom. Therefore, the new frontier in symptom management research is the evaluation of symptom clusters. This presentation will provide an overview of the field of symptom cluster research. The evolving definition of a symptom cluster will be discussed and methodologic approaches to symptom cluster research will be described. In addition, this presentation will summarize recent findings from symptom cluster research that can be used in clinical practice. Current research findings in symptom cluster research suggest that the development of symptom clusters depends on the patient's cancer diagnosis as well as the type of cancer treatment the patient receives. In addition, recent evidenced suggests that some symptoms within a specific symptom cluster are relatively stable across a course of cancer treatment. The presentation will conclude with a discussion of future directions for research on symptom clusters.