cells could play a role in cancer progression. When analysing the expression of BE in 30 human melanoma biopsies obtained from patients, we found a correlation between beta endorphin expression and stage of the malignancy (p < 0, 05). We analysed the potential role of BE in preventing immune response against tumor cells and performed a mice model of cancer progression by subcutaneous injection of melanoma B16 cells to both mu opioid receptor deficient mice (MOR -/-) and their WT counterparts. A profound decrease in tumor growth was observed in MOR -/- mice compared to WT animals (median volume 0,2 cm3 versus 0,8 cm3 at day 15 post injection; p < 0,01). This was paralleled by a significant higher infiltration of CD4+, CD8+, NK and dendritic cells at tumor site of MOR -/- mice determined by flow cytometry and immunohistochemistry. Adoptive transfer experiment with PKH-26-labeled MOR -/- leukocytes in combination with PKH-67-labeled WT leukocytes demonstrated that the higher presence of immune cells was not du to a higher recruitment of cells at tumor sites, but rather to proliferation and activation of leukocytes. NK cell activation was indeed increased by the use of BE-blocking antibody.

These findings demonstrate that endgenous beta endorphin secretion by melanoma cells plays a role in tumor growth and immune escape. Blocking beta endorphin therefore appear to be a promising new attractive therapeutic strategy to limit cancer progression.

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The monocarboxylate transporter 1 (MCT1) and Hypoxia-induced MCT4 are key targets promoting tumor cell survival

J. Chiche[1], R. Le Floc'h[1], D. Roux[1], J. Pouysségur[1]
[1]*Centre Antoine Lacassagne (CLCC), Institut de Biologie du Développement et Cancer, Nice, France*

In the hypoxic tumor microenvironment, cancer cells switch their glucose metabolism to glycolysis for their energy demands. This is known to generate a large amount of lactic acid that must be rapidly exported to maintain a permissive intracellular pH, essential in sustaining glycolysis, protein synthesis and cell survival. Cells have evolved several transport systems to extrude lactic acid. A large family of H+-linked MonoCarboxylate Transporters, represented by the ubiquitously expressed MCT1, co-transport H+/lactate- in both directions. Interestingly, MCT4, a member of this family widely expressed in tumor cells, is up-regulated in hypoxia by the transcription factor HIF. In addition, the functional expression of MCT1 and MCT4 in the plasma membrane is finely regulated by specific interaction with the glycoprotein chaperone CD147/Basigin.

Why do tumor cells co-express two lactate transporters? What are their respective functions? Are they both essential for tumor metabolism?

Firstly, we show in Ras-transformed fibroblasts, which express only MCT1, that blockade of this transporter (siRNA or AstraZeneca inhibitor) severely restricts cell growth and survival in vitro in hypoxia and in vivo in xenografted tumors in nude mice. Secondly, we show that ectopic expression of MCT4 in these Ras-transformed fibroblasts bypasses the MCT1 blockade. MCT4 expression restored ATP levels and growth in vitro in hypoxia and in vivo, induced tumors to escape the block in MCT1. Thirdly, we demonstrate that silencing CD147 or MCT4 in several human tumor cell lines grown in hypoxia (breast, prostate, colon, head & neck, melanoma) induces rapid cell death when MCT1 is co-inactivated.

We therefore conclude that MCT1 and MCT4 are two key steps in hypoxic tumor metabolism and as such represent new targets for anticancer therapy.

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Hypoxia-induced BNIP3 reduces proliferation of colon carcinoma cells through downregulation of ERK1/2

R. Garcia-Medina[1], N. Mazure[1], E. Vial[1], J.C. Chambard[1], J. Pouyssegur[1]
[1]*Centre Antoine Lacassagne, 6543 CNRS, Nice, France*

The development of solid tumors is often accompanied by the appearance of hypoxic regions. Tumor cells rapidly respond to this new micro-environment by activating the Hypoxia-induced transcription factor HIF, an acknowledged strong promoter of tumor growth. HIF activates a complex gene expression program ensuring cell survival by inducing glycolysis, angiogenesis, autophagy, migration and invasion but also by controlling proliferation. Amongst these adaptive processes the control of tumor cell proliferation by hypoxia remains unclear and largely uncharacterized at the molecular level. We present here new evidence confirming the negative impact of hypoxia (1% O2) on cell proliferation. We also provide proof that the hypoxia-induced HIF-1a gene known as Bcl2/adenovirus E1B 19kDa-interacting protein 3 (BNIP3) does not induce cell death but mediates the decrease in tumor cell proliferation induced by hypoxia. We demonstrate, in both non-tumoral fibroblast (CCL39) and colon carcinoma (BE) cell lines, that BNIP3 triggers a decrease in the level of phosphorylated ERK leading to a substantial increase in the accumulation of the CDK inhibitor p27 and a delay in S-phase entry. We show that inhibition of ERK activity by treatment with the MEK inhibitor U0126 abolished the hypoxic and HIF-1-induced expression of BNIP3 suggesting the existence of a negative feedback loop regulating BNIP3 expression and cell proliferation in tumors. We propose that hypoxia-induced BNIP3 participates in the general HIF-induced adaptive mechanism leading to tumor cell survival through the attenuation of the rate of cell proliferation but also through the activation of autophagy (see Mazure et al. abstract).

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Caveolin-1, a novel Id1 binding partner, and its role on Id1-induced behavioral change in prostate cancer cells

Y.C. Wong[1], X.M. Zhang[1], M.T. Ling[1], X.H. Wang[1]
[1]*University of Hong Kong, Department of Anatomy, Hong Kong, China*

Id-1 (Inhibitor of Differentiation/DNA binding-1) is reported to promote cell proliferation, invasion and survival in many types of human cancer cells through multiple signaling pathways. However, how Id1 interacts with these pathways and the immediate downstream effectors of the Id1 protein are not known. In this study, we identified a novel Id-1 interacting protein, caveolin-1 (Cav-1), a cell membrane protein and a positive regulator of cell survival and metastasis in prostate cancer. Using immunoprecipitation method, we found that the helix-loop-helix domain of the Id-1 protein was essential for the physical interaction between Id-1 and Cav-1. We also demonstrated in prostate cancer cells that the physical interaction between Id-1 and Cav-1 played a key role in the Id-1-induced epithelial-mesenchymal transition and cell migration as well as resistance to taxol-induced apoptosis. Our results also revealed that the Id-1-induced Akt activation through promoting the binding activity between Cav-1 and protein phosphatase 2A was responsible for the synergistic effect between these two proteins. Our study demonstrates a novel Id-1 binding partner and suggests a molecular mechanism that mediates the function of Id-1 in promoting prostate cancer cell invasion and survival through activation of the Akt pathway [(HKU7478/03M) to XHW and YCW (HKU7490.03M, 7470/04M, NSFC/RGC N_HKU738/03, HKU Foundation Seed Fund, 03)].

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SEMA3F Semaphorin is involved in tumor angiogenesis

J. Roche[1], V. Potiron[2], P. Nasarre[3], G. Sharma[3], R. Gemmill[3], H. Drabkin[3]
[1]*CNRS UMR 6187, Faculté des Sciences de Poitiers, Poitiers, France;* [2] *CNRS UMR 6187 and MUSC, Faculté des Sciences de Poitiers, Poitiers and Charleston SC, France;* [3] *MUSC, Division of Hematology-Oncology, Charleston SC, USA*

Class-3 semaphorins (SEMA3s) and VEGF are secreted proteins that bind neuropilin receptors suggesting antagonism, although recent studies argue against binding competition. In addition, SEMA3s regulate integrin activation in the vascular system, as well as in tumor cells.

SEMA3F was identified as a tumor suppressor in lung cancer by chromosome mapping of heterozygous deletions. We and others subsequently demonstrated that SEMA3F blocks in vivo tumorigenesis using different animal models. This was associated with inhibition of integrin-mediated attachment and reduced angiogenesis.

We studied intracellular signaling changes due to overexpression of SEMA3F in H157 lung cancer cells and found lower activity of ILK, ERK1/2, AKT and STAT3. Importantly, we observed downregulation of HIF-1α protein, along with VEGF transcription reduction. In a mouse subcutaneous tumorigenesis model, SEMA3F overexpression had a growth-inhibitory effect that was coupled with reduced vascular support. To further our investigations, we adapted the chick chorioallantoic membrane (CAM) assay to test the angiogenic capacity of lung cancer cells transfected with SEMA3F or VEGF165. Our results confirm the anti-angiogenic activity of SEMA3F but also suggest that VEGF repression at the level of transcription is only partially responsible for the inhibition of angiogenesis. Moreover, VEGF stable transfection in SEMA3F-expressing lung cancer cells did not reverse the inhibitory action of SEMA3F on phospho-ERK1/2.

These data suggest that VEGF antagonism by SEMA3F might not explain all of its anti-tumorigenic properties, and thereby support the development of SEMA3F as a therapeutic agent in cancer.

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The effect of covalent linkage and the number of Arg residues on the in vitro cytostatic effect and cellular uptake of daunomycin-conjugates on HepG2 and HL-60 tumour cells

E. Orbán[1], Z. Miklán[1], G. Schlosser[1], F. Hudecz[1]
[1]*Eötvös Loránd University, Research Group of Peptide Chemistry Hungarian Academy of Sciences, Budapest, Hungary*

Daunomycin (Dau) is an anthracycline derivative widely used in cancer chemotherapy. Dau inhibits the growth and division of the cells mainly by