ossification centers and delta phalanx. DBQD type 1 is caused by mutations in Calcium-Activated Nucleotidase 1 (CANT1), while DBQD type 2 by mutations in xylosiltransferase 1 (XYLT1).
CANT1 is a nucleotidase present in the ER/Golgi that preferentially hydrolyzes UDP, suggesting its involvement in protein glycosylation and in proteoglycan metabolism.
To better investigate CANT1 role in the etiology of DBQD, we generated a Cant1 knock-in (KI) mouse carrying the R302H substitution reproducing the R300H mutation already observed in patients and a Cant1 knock-out (KO) mouse by excision of exon 3 and 4.
Double staining with alcian blue and alizarin red demonstrated that KI mice are smaller with shorter and thinner tibiae, femurs and ilia compared to the wild-types. In limb extremities of KI mice the same hand anomalies present in DBQD patients were observed. At the morphological level KO mice showed growth defects and typical skeletal anomalies already observed in KI mice and patients. These results demonstrated that both mouse strains develop a skeletal phenotype reminiscent of DBQD type 1. Proteoglycan (PG) metabolism was studied in chondrocytes from KO mice. To study PG synthesis, chondrocytes were labeled with 35S-sulfate and the amount of newly synthesized PGs was evaluated: reduced synthesis of PG was observed in KO chondrocytes compared to wild-type cells both in presence or in absence of β-D-xyloside, an enhancer of glycosaminoglycan (GAG) synthesis. Moreover, the hydrodynamic size of GAGs was investigated by gel chromatography demonstrating that GAGs from KO chondrocytes were smaller in size than wild-type ones. Pulse-chase labeling of chondrocytes showed reduced PG secretion in KO cells compared to wild-types. This result was confirmed by electron microscopy demonstrating the presence in KO chondrocytes of huge vacuoli containing proteinaceus material.
In conclusion we generated and validated a KI and a KO mouse as animal models of Desbuquois Dysplasia type 1 and we demonstrated that CANT1 plays a role in PG metabolism.
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DIFFERENTIAL INFLUENCE OF HYPOXIA ON GENE EXPRESSION OF TUMORAL AND NON TUMORAL MAMMARY CELLS

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Cancer metastasis is the result of a series of deregulated biological phenomena, including alterations of cell-cell and cell-matrix interactions and of other microenvironmental conditions such as the oxygen tissue supply. Hypoxia is a well-known driver of aggressive cancer phenotypes, indeed tumors with poor prognosis have higher proportions of anoxic and hypoxic areas[1]. The consequences of tumour hypoxia can be local or even systemic towards distant organs, and it can evoke diversified responses: whereas low *oxygen concentration in tissue* environments. (pO_2 <7 mmHg) exerts anti-proliferative effects and promotes differentiation, apoptosis and/or necrosis on normal cells, the tumoral cells react to hypoxic stress with adaptive processes that confer them an aggressive phenotype[2]. Indeed, the hypoxic microenvironment in tumors contributes to alter energy metabolism, cell growth and responsiveness to therapy.
The aim of present study was the identification, by a proteomic strategy, of the effects exerted by hypoxic conditions on the 8701-BC breast cancer cells compared with HB2 immortalized normal mammary epithelial cells. For this purpose, the two cell cultures, were grown at low oxygen content (pO_2=2%) in parallel with normoxic cells (pO_2=20%).
Hypoxic and normoxic cells at confluence were then properly collected, lysed and subjected to 2D-IPG based proteomic analysis[3]. Proteins identified by several methods[4] were then clusterized by using the gene ontology database DAVID. The results showed that the hypoxic condition exerts different effects on the proteomic profile of the two cell lines.
In particular, a general down-regulation of the proteome complement was observed for the HB2 cells and especially for the classes of the negative regulators of apoptosis and of the proteins involved in membrane vesiculation. Conversely, the proteomic profile of the 8701-BC cells was not altered significantly by the hypoxia, except for the highly modulated protein class of the cytoskeleton.
These data suggest that hypoxia may depress cell behaviour of non-tumoral cells, while is ineffective on neoplastic cells, basically adapted to anaerobic metabolism, or even promotes cell motility which contributes in directing the tumour cells to acquire a more aggressive phenotype.

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HIPK2 AND HEPARANASE : NEW PLAYERS IN RENAL FIBROSIS

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characterized by the accumulation of extracellular matrix that when persists can lead to organ failure. A key event in tubulointerstitial fibrosis is the epithelial-to-mesenchymal transition (EMT) of tubular epithelial cells into myofibroblasts. In the kidney, EMT is triggered by several factors: hypoxia, reactive oxygen species, advanced glycation end products and numerous profibrotic cytokines and growth factors such as FGF-2 and TGF-β. Homeodomain-interacting protein kinase 2 (HIPK2) is a conserved serine/threonine nuclear kinase that regulates gene expression by phosphorylating transcription factors and accessory components of the transcription machinery. The dysregulation of HIPK2 can result in p53 dysfunction and augmented proliferation of cell population as it occurs in cancer and fibrosis. Recently, it has been shown that HIPK2 is a master regulator of kidney fibrosis in experimental models of chronic kidney diseases (CKD)[1].
Several experimental data also support the involvement of heparanase (HPSE) in the pathogenesis of kidney fibrosis. HPSE is an endoglycosidase that cleaves heparan sulfate (HS) chains and participates in ECM remodeling and degradation as well as in the regulation of the release from ECM storages of HS-bonded molecules. Recently we provided evidence that HPSE is specifically involved in the establishment of tubular fibrosis, being necessary for the epithelial-mesenchymal transition (EMT) of tubular cells induced by FGF-2 and TGF-β[2,3]. Starting from these evidences, we aimed to characterize the role of HIPK2 as fibrosis regulatory molecule and the possible link between HIPK2 and heparanase in pro-fibrotic condition. In