this fuel, tumors shunt their metabolic flux more toward glycolysis than normal cells, a strategy that allows for tumor survival when oxygen is limiting. Also, the resultant lactic acid poisons their extracellular environment facilitating invasion and metastasis. Significantly, tumors harness a crucial enzyme to support this destructive path — to entrap and channel glucose toward glycolysis. This enzyme is HK-2 an isoform of hexokinase. Due to many-faceted molecular features including genetic, epigenetic, transcriptional, enzymatic and sub-cellular localization to mitochondria, HK-2 facilitates and promotes the high glycolytic tumor phenotype. Thus, HK-2 represents a pivotal model gene or enzyme that tumors "select for" during tumorigenesis. In this lecture, the speaker will describe both the pivotal roles played by mitochondrial bound HK-2 and show also how the small molecule 3-bromopyruvate, an inhibitor of both HK-2 and mitochondrial function selectively eradicates such tumors while sparing normal tissues.

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Recent Review:

Mathupala SP, Ko YH, Pedersen PL (2009) *Semin. Cancer Biol.* **19**: 17–24.

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PL.10

Import and assembly of mitochondrial proteins

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Most mitochondrial proteins are synthesized as precursors on cytosolic ribosomes and imported into the organelle. The translocase of the outer membrane (TOM complex) forms the main entry gate for the majority of precursor proteins. The precursors are subsequently distributed to the four mitochondrial subcompartments. Recent studies revealed a remarkable variety of different pathways and mechanisms for protein sorting in mitochondria. (i) The presequence pathway can transport preproteins into the matrix, inner membrane and intermembrane space of mitochondria. The presequence translocase of the inner membrane (TIM23 complex) cooperates with the import motor PAM. The mitochondrial processing peptidase and further enzymes cleave the preproteins to remove the presequences and generate mature proteins. (ii) The carrier pathway directs multispanning hydrophobic proteins into the inner membrane, using the Tim9–Tim10 chaperone complex of the intermembrane space and the carrier translocase of the inner membrane (TIM22 complex). (iii) Many intermembrane space proteins are imported by a redox-regulated machinery (MIA), involving disulfide-linked intermediates between the intermembrane space receptor Mia40 and precursor proteins. (iv) Protein insertion into the mitochondrial outer membrane involves different pathways for beta-barrel proteins and alpha-helical proteins. Beta-barrel proteins are inserted into the membrane by the sorting and assembly machinery (SAM complex).

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PL. 11

Mitochondria, calcium signaling and cell death by apoptosis and autophagy

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Mitochondria rapidly accumulate Ca^{2+} through a low-affinity uptake system (the mitochondrial Ca^{2+} uniporter, MCU) because they are exposed to high [Ca^{2+}] microdomains generated by the opening of ER Ca^{2+} channels. These rapid [Ca^{2+}] changes stimulate Ca^{2+}-sensitive dehydrogenases of the mitochondrial matrix, and hence rapidly upregulate ATP production in stimulated cells. Ca^{2+} also sensitizes to cell death mediators, e.g. ceramide. Accordingly, we demonstrated that Bcl-2 reduces the state of filling of ER Ca^{2+} stores, and this alteration is effective in reducing the sensitivity to apoptotic challenges. I present data on: 1) The effect on mitochondrial Ca^{2+} homeostasis of other signalling pathways involved in autophagy and apoptosis (Akt, sirt3). 2) The signalling route that links oxidative stress to the activation of p66shc, an isoform of a growth factor adapter acting as apoptotic inducer. PKCβ, activated by the oxidative challenge, induces p66shc phosphorylation, with ensuing alteration of mitochondrial structure and function. We also showed that this route is involved also in adipose differentiation of muscle-derived precursors, highlighting a novel process of utmost interest in pathophysiological conditions. 3) The molecular elements of the mitochondria–ER Ca^{2+} connection. I will discuss the role of VDAC in rapidly channelling Ca^{2+} through the outer mitochondrial membrane and the specific functions of VDAC isoforms in autophagy and apoptosis.

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PL. 12

Mitochondrial transhydrogenase — New aspects of its physiological role

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Mitochondrial nicotinamide nucleotide transhydrogenase (Nnt) catalyzes the reduction of $NADP^+$ by NADH giving NADPH and NAD^+, driven by the electrochemical proton gradient, Δp. Together with $NADP^+$-isocitrate dehydrogenase ($NADP^+$-ICH) and $NADP^+$-dependent (decarboxylating) malic enzyme (MAEB), Nnt constitutes one of the major providers of NADPH. Knockout and inhibition studies in *C. elegans* [1] and intact heart cells [2] have indicated that, as expected and previously proposed [3], the high NADPH/$NADP^+$ ratio generated by Nnt ensures a high mitochondrial GSH/GSSG ratio through the glutathione reductase (GR) reaction (for a review, see ref [4]). Recently, the commonly used C57BL/6J mouse strain was shown to harbour a mutated NNT gene, probably introduced in the 1950´s, rendering an incomplete and inactive Nnt. This C57BL/6J mouse