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The bioenergetic signature of cancer

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Cancer is a heterogeneous and complex genetic disease. In addition to genetic mutations in oncogenes and tumour suppressors, the onset and progression of cancer is also bound to the cancer cell's microenvironment. After many years of ostracism the energetic metabolism of cancer [1] has been accepted as an additional hallmark of the cancer phenotype [2] and mitochondrial/glycolytic studies have spurred in the field. In this regard, it has been reported that the relative expression of β-F1-ATPase, which is the catalytic subunit of the mitochondrial H^+-ATP synthase and thus a rate-limiting component of mitochondrial oxidative phosphorylation, is significantly diminished in human tumours when compared to its expression in normal tissues [2]. The down-regulation of β-F1-ATPase is accompanied by an increased expression of GAPDH, a marker of glycolysis. The tumour drop in the β-F1-ATPase/GAPDH ratio, that defines the *"bioenergetic signature"* of the cell [3], is a phenotypic trait fulfilled by more than 95% of the carcinomas analyzed in large cohorts of breast, colon and lung cancer patients [2]. These findings support a deficit in the overall bioenergetic activity of mitochondria in cancer. The quantification of the *bioenergetic signature* in different human carcinomas revealed that, irrespective of the cancer type, energy metabolism has a unique protein signature [4], thus providing a generic marker of the cancer cell that might be exploited in the combat of the disease [2]. The *bioenergetic signature* also has clinical relevance as an indicator of disease progression and as a predictive marker of the cellular response to chemotherapy [2]. Moreover, the *bioenergetic signature* affords a gauge of the glycolytic activity of the tumours, supporting that an altered oxidative phosphorylation is one of the determinants that underlies the abnormal aerobic glycolysis of the cancer cell [5].

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The specific repression of β-F1-ATPase mRNA translation partially explains the abnormal bioenergetic activity of mitochondria in colon, lung and breast tumours [6] as well as in hepatocarcinomas [7]. By manipulation of the *bioenergetic signature* in cancer cells we have documented that tumour promotion inevitably requires the selection of cells with a repressed bioenergetic activity of mitochondria [8]. In others words, cancer cells with a functional bioenergetic activity of mitochondria are unable to promote tumour development. In this presentation, I will summarize some of the findings that stress that cancer progression requires the silencing of the bioenergetic activity of mitochondria, emphasize its potential value for translation to the bed-side and discuss some of the strategies that we are developing aimed at identifying the players that participate in the regulation of the bioenergetic signature of the cancer cell.

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