C2M2NF, A core model of central metabolism with Carbon, Nitrogen and Folate pathways: application to One-carbon metabolism in cancer cells.

Jean-Pierre Mazat Univ. Bordeaux, CNRS, IBGC, UMR 5095, F-33000 Bordeaux, France

université de BORDEAUX

Cancéropôle Grand Sud-Ouest

CNRS dépasser les frontières

AFMTÉLÉTHON CURE THROUGH INNOVATION

INTRODUCTION : 1C-metabolism is crucial for several syntheses (purine etc.)in proliferating cells. Thus it is the object of intense research for anti-tumor drugs.

I THE SALIENT FEATURES OF 1C-METABOLISM IN CANCER CELLS

1 - Serine is the main 1C donor in cancer cells mainly for purine synthesis

2 - The folate metabolism is predominantly mitochondrial (purine synthesis is cytosolic) SHMT2, MTHFD2, MTHFD1L and in part of the cases ALDH1L2 are overexpressed. SHMT1, MTHFD1 and ALDH1L1 are underexpressed.

3 - Serine deprivation slows down the growth
Rescued by serine or formate

4 - Output of formate as hallmark of oxidative cancer ?

5 - Production of NADPHm and NADHm in mitochondria ?

6 - Substrate level phosphorylation (ATPm production) with formate production

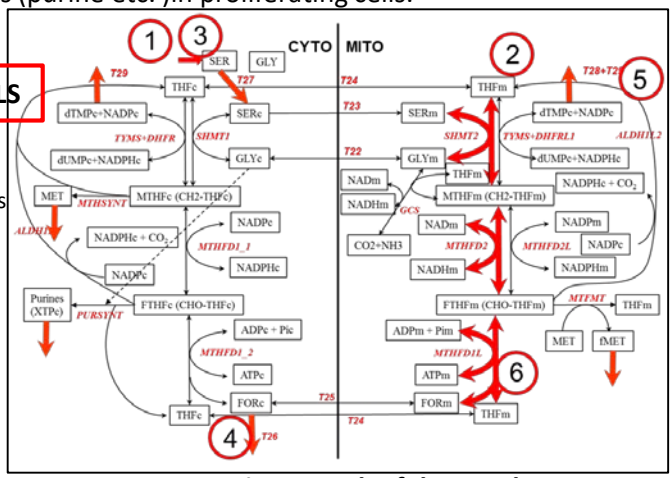
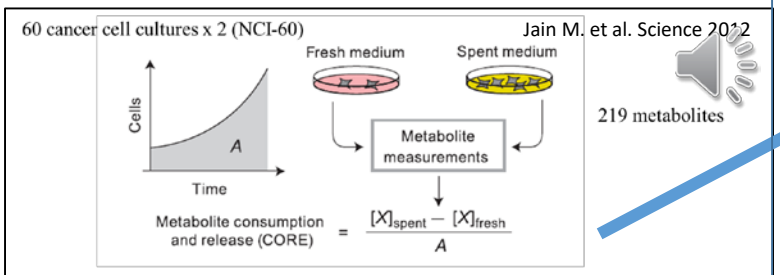


Figure 1: The folate cycles

II THE « AVERAGE CANCER CELL»



Metabolite	glucose	lactate	glutamine	glutamate	serine	glycine	alanine	IV Thr+Ile+Va	YFLKW
Mean	-304,67	427,49	-74,48	12,02	-11,08	1,23	15,04	-13,70	-18,34
Std. Deviation	207,49	252,16	52,86	11,91	7,45	2,99	12,77	8,09	10,71

Figure 2: The main average input/output fluxes

III RESULTS

Objective function: Max of the Biomass
Constraints
- Input of Glucose, glutamine and serine
- Output flux of lactate, glutamate and glycine
- Import of Am. Ac.

Results
. High aerobic glycolysis
.Krebs cycle mainly reduced to citrate production
. High Oxphos with high ATP production (Production of ATP is not a problem)
. IDH1 => NADPHc
. (- IDH3) => NAD (reducing glutaminolyse)

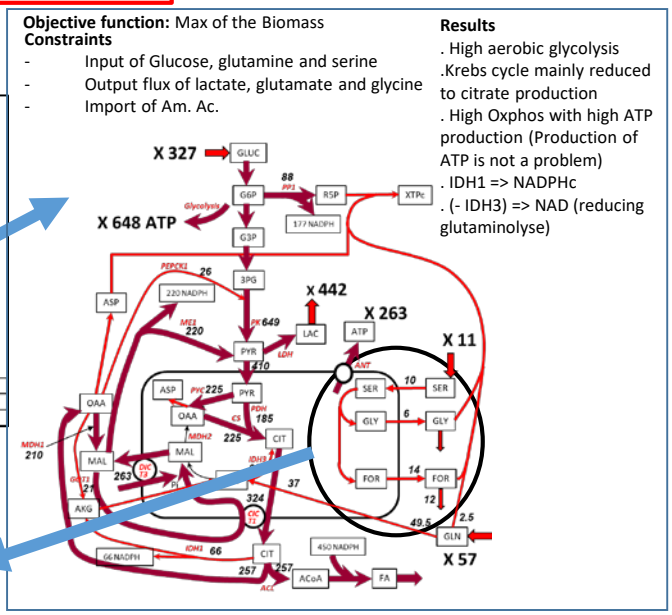


Figure 3: The metabolism of the « average cancer cell »

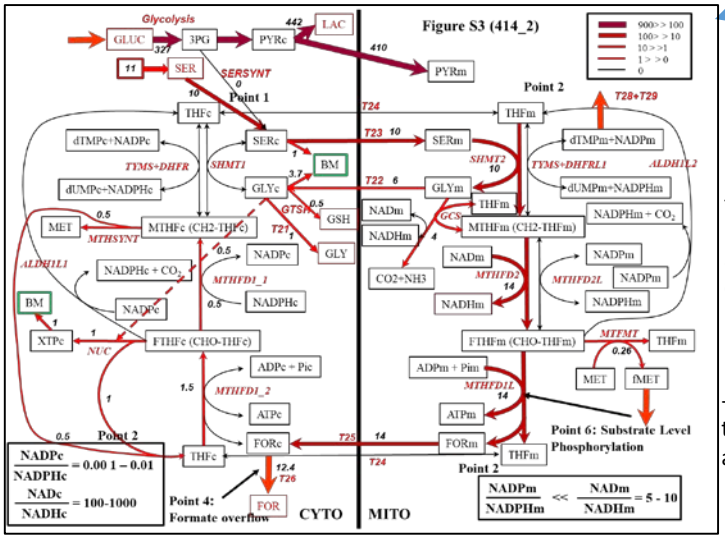


Figure 4: The fluxes in the folate cycles

CONCLUSIONS

– NADH: Catabolism of proliferating cells generates NADH the accumulation of which opposes the proliferation that created it. ***Elimination of NADH (to NAD) is the big problem of proliferating cells***. All means are being employed to this aim, for instance:
NADHm -> NADPc with IDH1
(-IDH3) and cycling of 1C metabolism between cytosol and mitochondria.
- The NAD(P) / NAD(P)H ratios appear as the main dispatchers between the different metabolic pathways in balancing the substrates/products associated with the couples NAD(P) / NAD(P)H

REFERENCES

[1] Mazat J.-P. Biochemical Society Transactions 2021
[2] Mazat J.-P. and Ransac S. Metabolites 2019.