Towards the identification of a complex signaling network coupling carbon metabolism and DNA replication

Anne-Françoise Monnier[1], Hamid Nouri[1], Monika Maciag[2], Solveig Fossum-Raunehaug[3], Gregorz Wegrzyn[2], Kirsten Skarstad[3], Agnieszka Szalewska-Palasz[2] and Laurent Jannière[1,4].

1 : Laboratoire de Génétique Microbienne, INRA, 78350 Jouy en Josas, France
2 : Department of Molecular Biology, University of Gdańsk, 80822 Gdańsk, Poland
3 : Department of Cell Biology, Institute of Cancer Research, Norwegian Radium Hospital, Rikshospitalet, University of Oslo, 0310 Oslo, Norway
4 : Corresponding author (laurent.janniere@jouy.inra.fr)

Models of life evolution posit that cells originate from molecular catalysts that emerged hand-in-hand in confined environments in the prebiotic world to form networks of interactions capable of coordinated activities. From these networks the biosynthetic machineries of modern cells evolved to ensure vital processes like central carbon metabolism and DNA synthesis.

Consistent with these models, it has been established that DNA synthesis is tightly coupled to central carbon metabolism in all organisms. In bacteria, this coupling is achieved by modulating the initiation frequency and the time required to replicate the chromosome. Despite a long history of study, the mechanism at play has resisted molecular insight. This is an indication of its complexity which likely results from the long period of co-evolution.

We recently uncovered a strong genetic link between five reactions of central carbon metabolism (the terminal reactions of glycolysis) and three replication enzymes (the helicase, the primase and the lagging-strand polymerase, DnaE) in steady-state cells of the bacterium *Bacillus subtilis* (1). Here, we present a study aimed at looking for replication defects in metabolic mutants. Our results show that cells mutated in the terminal reaction of glycolysis over-initiate DNA synthesis and that this phenotype likely results from an alteration of the carbon flux through the terminal glycolytic reactions. Interestingly, neither the over-initiation phenotype nor the previously described genetic link depend on ppGpp, an alarmone that signals cell metabolic status and that is supposed to be involved in the metabolism-replication coupling.

The results presented here and previously (1) thus suggest that we have identified for the first time elements of the metabolism-replication coupling: the terminal reactions of glycolysis and three replication enzymes (the helicase, the primase and the lagging-strand polymerase DnaE). They also suggest that coupling depends on the carbon flux passing through glycolysis but not on ppGpp and that it involves metabolism-driven changes in replication enzymes. Thus, the metabolism-replication coupling might be orchestrated by a complex regulatory network involving various signalling molecules. Possible mechanisms will be discussed.

(1): Jannière L ., Canceill D., Suski C., Kanga S., Dalmais B., Lestini R., Monnier A.-F., Chapuis J., Bolotin A., Titok M., Le Chatelier E. et Ehrlich S. D. (2007) Genetic evidence for a link between glycolysis and DNA replication ***PLoS ONE*** 2(5) :e447.