Iron-Dependent Cellular Programming of Mixed-Carbon Utilization, Carbon Metabolism, and Siderophore Yield in a Soil Bacterium

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Soil bacteria require ample iron (Fe) supply to meet the demand for Fe-containing catalytic cofactors in metabolic enzymes. However, aerobic bacteria including *Pseudomonas* species are often subjected to iron limitation in their nutritional environments due to the low solubility of Fe hydroxides and oxides. To overcome this limitation, these bacteria secrete high-affinity Fe-scavenging molecules or siderophores, which are expensive to the carbon metabolism. Therefore, an intimate balance between carbon utilization, metabolism, and siderophore biosynthesis is required for the survival of aerobic bacterial cells in Fe-limited environments. We investigated this balance as a function of Fe availability in the model soil bacterium *P. putida* KT2440 during growth on a mixture of sugar and aromatic substrates. We uncovered an emerging hierarchy in carbon utilization from the substrate mixture as a function of decreasing Fe supply. By contrast to Fe-replete *P. putida*, which exhibit no preference between the two substrate types, Fe-limited *P. putida* preferentially assimilate the aromatic substrate over the sugar substrate. Stable isotope-assisted metabolomics with ^{13}C tracer experiments revealed that, in response to Fe limitation, *P. putida* reprograms metabolic pathways to achieve (1) enhanced carbon fluxes towards metabolite precursors for siderophore biosynthesis and (2) a favorable coupling between Fe scavenging and preferential carbon metabolism. We found that a consequence of this cellular programming is the mobilization of µmolar Fe from Fe-bearing minerals.

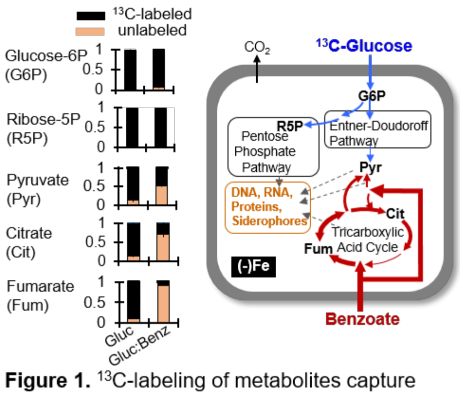

Figure 1. ^{13}C-labeling of metabolites capture carbon assimilation of glucose (Gluc) and unlabeled benzoate (Benz) into distinct metabolic pathways.