PROMISCUITY, SERENDIPITY AND METABOLIC INNOVATION

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Bioinformatic evidence suggests that metabolic pathways have evolved by “patchwork” recruitment of enzymes that have a promiscuous ability to catalyze a newly important reaction. However, we cannot explain why certain pathways arose rather than the thousands of other possibilities. Further, we have little insight into the *process* by which novel pathways were patched together and flux was improved via mutations.

We are studying the assembly of a novel pathway using a strain of *E. coli* in which *pdxB*, a gene required for synthesis of the cofactor pyridoxal 5’-phosphate (PLP), has been deleted. Because this strain cannot synthesize PLP, it cannot grow on glucose as a sole carbon source. We have evolved several lineages of the Δ*pdxB* strain in 0.4% glucose that can grow robustly on glucose. Each evolved strain has acquired 4-6 mutations. We have identified a four-step pathway patched together from promiscuous enzymes that bypasses the break in the PLP synthesis pathway caused by loss of PdxB (Fig. 1). We have identified the mechanisms by which three of the most common mutations in the adapted strains improve growth. We have also evolved several lineages of the Δ*pdxB* strain in 0.2% glucose. These strains show a strikingly different pattern of mutations, suggesting that they have either evolved a different mechanism to compensate for loss of PdxB, or have arrived at the same solution via a different evolutionary trajectory.

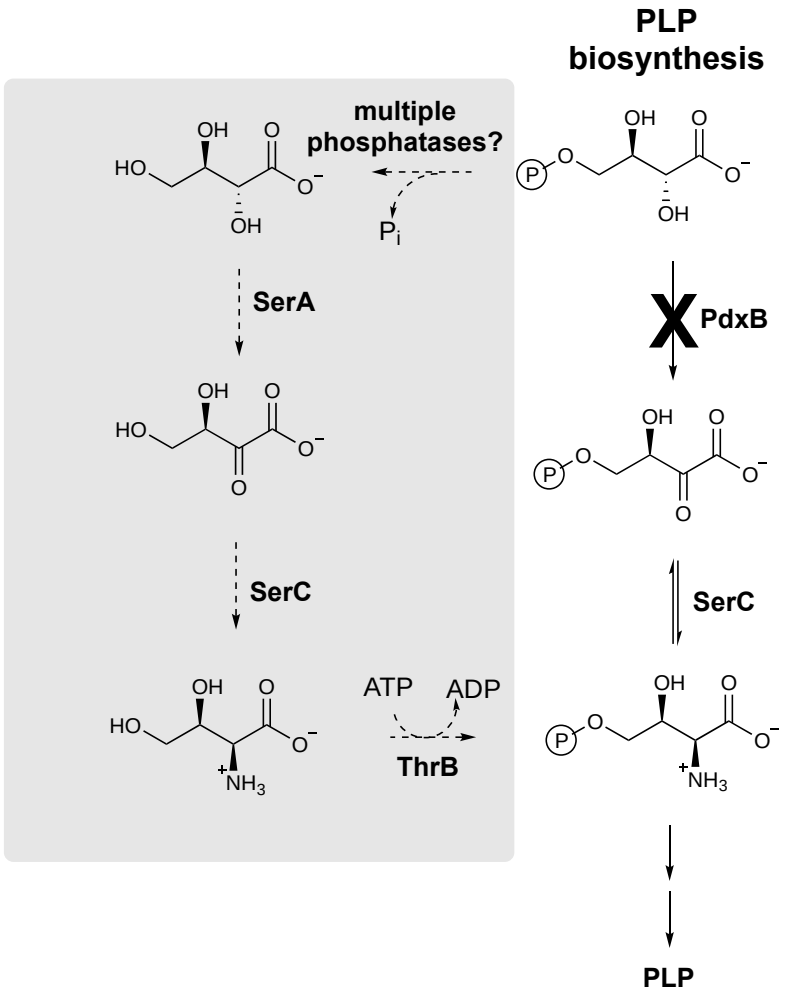

Fig. 1. A four-step pathway patched together from promiscuous activities of enzymes that normally serve other functions can bypass the break in PLP synthesis caused by loss of PdxB.