An integrated Whole-genome Interaction Network
of *Lactococcus lactis* for Metabolic Functional Design
以整合性乳酸菌全基因體交互作用網絡進行代謝功能設計

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Although many experimental and computational studies have been done on lactic acid bacteria, there is no report on combining all the networks of biological processes as a whole. To understand the cellular dynamics of lactic acid bacteria from signal sensing and nutrient transporting to a cascade of reactions inside the cells, we used *Lactococcus lactis* IL-1403 as a model organism to investigate the relations among the genes to realize the complete 'biological activity map' resided in it. Different types of molecular interactions were used to construct this **I**ntegrated **N**etwork of *Lactococcus lactis* (**INLA**), including (a) signal transduction and transporter systems; (b) gene regulations by transcriptional factors (DNA-protein interactions); (c) protein-protein interactions and (d) metabolic pathways. In order to improve the completeness of this integrated infrastructure, the mapping of orthologous protein-protein interactions were used to make connections for many missing relations. INLA comes with many interconnected genes based on our proprietary database of functional relationships extracted from both scientific literature and bioinformatics analysis, and works from leading public databases of pathways. We attempted to see if genes with multiple connections (network hubs) are more important and essential more often than those poorly connected genes. The percentage of essential genes was estimated and used to examine various phenotypes based on this integrated interaction network. Further deletion of selected genes should not only reveal that whether a gene is essential or not, but also show if natural selection has preferentially kept these genes required for vital functions. More investigations will disclose if many of the important genes appeared in *Lactococcus lactis* have remained conserved in other prokaryotic species. This integrated interaction network is expected to provide biologists with a comprehensive knowledge resource on experimental perturbations of target genes in the lactic acid bacteria model organism. The biotechnology applications of our **I**ntegrated **N**etwork of *Lactococcus lactis* (**INLA**) and their molecular regulation mechanisms for metabolic design of desired microbial metabolite production will be discussed in this report.