L-Arginine and L-Citrulline: Production Technology in Genomic Era

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L-Arginine, a semi-essential amino acid, has lately attracted considerable attention because the amino acid has been shown to be a precursor to nitric oxide (NO), a key component of endothelial-derived relaxing factor. Because of L-arginine's NO-stimulating effect, the amino acid helps, for example, to relax and dilate blood vessels, and thus can be utilized in numerous clinical areas. On the other hand, L-citrulline, a precursor of L-arginine biosynthesis, is also an important amino acid for our health since it is a source of endogenous L-arginine in the body. These two L-amino acids are produced by fermentation using classically derived regulatory mutants of *Corynebacterium glutamicum*, a representative amino acid-producing microorganism.

We previously developed a methodology to reengineer a more efficient producer using knowledge regarding the mutations that have accumulated over years of industrial strain development. In this methodology, biotechnologically useful mutations identified through the genome analysis of classical mutants are systematically introduced into the wild-type genome in a pinpointed manner, thus allowing creation of a defined mutant that carries only useful mutations. Furthermore, with the accumulated knowledge on mutations relevant to production, it becomes possible to combine positive mutations derived from different lines of classical producers in a single wild-type background. Such an advanced approach has recently led to an impressive result in production of L-arginine and L-citrulline by *C. glutamicum*. The procedure and impact of this reengineering methodology are described here.

This work has been arranged mainly based on the research fruits conducted with my co-workers, S. Mitsuhashi, J. Hayashi, K. Tanaka of Kyowa Hakko Bio Co.