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New insights in the molecular biology and physiology of *Streptococcus thermophilus* revealed by comparative genomics

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Abstract

Streptococcus thermophilus is a major dairy starter used for the manufacture of yoghurt and cheese. The access to three genome sequences, comparative genomics and multilocus sequencing analyses suggests that this species recently emerged and is still undergoing a process of regressive evolution towards a specialised bacterium for growth in milk. Notably, *S. thermophilus* has maintained a well-developed nitrogen metabolism whereas its sugar catabolism has been subjected to a high level of degeneracy due to a paucity of carbon sources in milk. Furthermore, while pathogenic streptococci are recognised for a high capacity to expose proteins at their cell surface in order to achieve cell adhesion or to escape the host immune system, *S. thermophilus* has nearly lost this unique feature as well as many virulence-related functions. Although gene decay is obvious in *S. thermophilus* genome evolution, numerous small genomic islands, which were probably acquired by horizontal gene transfer, comprise important industrial phenotypic traits such as polysaccharide biosynthesis, bacteriocin production, restriction–modification systems or oxygen tolerance.

Keywords: Streptococci; Metabolic pathways; Pseudogenes; Genome decay; Milk

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Contents

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1. Introduction

Streptococcus thermophilus is of major importance for the food industry since it is massively used for the manufacture of dairy products (annual market of around 40 billion USD) and it is considered as the second most important industrial dairy starter after *Lactococcus* (*Lc.*) *lactis* [1–3]. This bacterium belongs to the group of the thermophilic lactic acid bacteria and is traditionally used in combination with *Lactobacillus delbrueckii* subsp. *bulgaricus* (*Lb. bulgaricus*) or *Lb. helveticus* for the manufacture of yogurt and so-called hard "cooked" cheeses (e.g., emmental, gruyère, grana), at a relatively high process temperature (45 °C) [2,4]. *S. thermophilus* is always used together with *Lb. bulgaricus* for yogurt making, which led to development of a complex symbiotic relationship ("proto-cooperation") between these two partners sharing the same ecological niche [3,4]. *S. thermophilus* is also used alone or in combination with lactobacilli for the production of mozzarella and cheddar cheeses [2].

S. thermophilus is closely related to *Lc. lactis*, but it is even more closely related to other streptococcal species comprising several deadly human pathogens (e.g., *S. pneumoniae*, *S. pyogenes*, *S. agalactiae*), which cause for example pneumonia, bacterial sepsis or meningitis [5,6]. *S. thermophilus* is also related to *S. mutans*, the most important pathogen in tooth decay. Nevertheless, *S. thermophilus* is a "generally recognised as safe" (GRAS) species and over 10^{21} live cells are ingested annually by the human population. Recently, the complete genome sequence of two yogurt strains (LMG 18311 and CNRZ1066) and a third incomplete genome sequence (strain LMD9) were made publicly available ([7], http://genome.jgi-psf.org/draft_microbes/strth/strth.home.html). The comparison of the *S. thermophilus* genomes with published genomes of streptococcal pathogens [8–13] highlights its relatedness to pathogenic species but also reveals that the most important determinants for pathogenicity are either absent or present as pseudogenes, unless they encode basic cellular functions [7]. This reinforced our view that the massive consumption of this bacterium by humans entails no health risk. Comparative genomics also revealed that evolution has shaped the *S. thermophilus* genome mainly through loss-of-function events, even if lateral gene transfer played an important role, revealing that the dairy streptococcus has followed a evolutionary path divergent to that of pathogenic