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Enhanced productivity of protease-sensitive heterologous proteins by disruption of multiple protease genes in the fission yeast *Schizosaccharomyces pombe*

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Abstract The creation of protease-deficient mutants to avoid product degradation is one of the current strategies employed to improve productivity and secretion efficiency of heterologous protein expression. We previously constructed a set of single protease-deficient mutants of the fission yeast *Schizosaccharomyces pombe* by respective disruption of 52 protease genes, and we succeeded in confirming useful disruptants (Idiris et al., Yeast 23:83–99, 2006). In the present study, we attempted multiple deletions of 13 protease genes, single deletions of which were previously confirmed as being beneficial for reducing extracellular product degradation. Using PCR-based gene replacement, a series of multiple deletion strains was constructed by multiple disruption of a maximum of seven protease genes. Effects of the resultant multiple deletion strains on heterologous expression were then measured by practical expression of a proteolytically sensitive model protein, the human growth hormone (hGH). Time profiles of hGH secretion from each resultant mutant demonstrated significantly enhanced hGH productivity with processing of the multiple protease deletions. The data clearly indicated that disruption of multiple protease genes in the fission yeast is an effective method for controlling proteolytic degradation of heterologous proteins particularly susceptible to proteases.

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