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Thesis/dissertation Title

Generation and potential application of fast-growing Saccharomyces cerevisiae mutants with constitutive unfolded protein response

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The endoplasmic reticulum (ER) is a cellular compartment in which secretory proteins are folded and lipidic molecules are produced. Dysfunction of the ER is called ER stress and is harmful for cells. In yeast cells including Saccharomyces cerevisiae, ER stress leads to conversion of the HAC1 mRNA to the spliced form (HAC1i), which is translated into a transcription factor that drastically changes the gene expression profile. This cellular response ultimately enhances ER functions and is named as the unfolded protein response (UPR). Therefore, artificial evocation of the UPR is anticipated to increase productivity of beneficial materials, such as heterologous secretory proteins and commercially valuable lipidic molecules, in the ER. However, unregulated UPR is known to be detrimental.

In the first chapter of this thesis, I confirmed the harmful effect of the unregulated UPR. S. cerevisiae cells constitutively expressing HAC1i mRNA (HAC1i cells), which exhibited a strong UPR even under non-stress conditions, grew considerably slowly. Furthermore, HAC1i cells frequently yielded fast-growing and low-UPR progeny.

Intriguingly, growth of HAC1i cells was fasten in the presence of weak ER stress that was induced by low concentrations of the ER stressor tunicamycin or by cellular expression of the ER-localized version of green fluorescent protein (GFP). I speculate that because of lack of ER-client aberrant proteins, the UPR improperly impairs normal cellular functions when inappropriately induced in unstressed cells.

HAC1i cells producing ER-localized GFP stably exhibited a strong UPR, carried a highly expanded ER, and abundantly produced triglycerides and heterogenous carotenoids. I anticipate that our finding can be applied to the high-yield production of valuable lipidic molecules using yeast cells, which is a hopeful next-generation technique.