[MS9-03] A bZip transcription factor with homo/heterodimer-induced DNA-binding preference

Matthias Wilmanns, Larissa Consani-Textor, & Vivian Pogenberg

EMBL Hamburg Unit, Notkestrasse 85, D-22603 Hamburg
Email: wilmanns@embl-hamburg.de

The ability of basic leucine zipper transcription factors for homo- or heterodimerization provides a paradigm for combinatorial control of eukaryotic gene expression. In a previous contribution, we have shown how deviations from the leucine zipper register lead to alterations in DNA-mediated hetero-dimerization of the Microphthalmia-associated transcription factor [1]. It has been unclear, however, how facultative dimerization results in alternative DNA-binding repertoires on distinct regulatory elements. To unravel the molecular basis of such coupled preferences we used the hematopoietic basic leucine zipper transcription factor MafB as a model, as this protein has a special capability for facultative hetero- heterodimerization with a limited set of other basic leucine zipper transcription factors. To allow direct molecular comparison, we first determined two high-resolution structures of MafB as a homodimer and as a heterodimer with c-Fos bound to variants of the Maf-recognition element. The two structures revealed several unexpected and dimer-specific coiled coil–heptad interactions. Based on these findings, we have engineered two MafB mutants with opposite dimerization preferences. One of them indeed showed an almost exclusive preference for MafB/c-Fos heterodimerization. In addition this variant enabled a selection of heterodimer-favoring over homodimer- specific Maf-recognition element variants, demonstrating that protein/protein and protein/DNA interactions are interconnected. Our data provide a new concept for transcription factor design to selectively activate dimer-specific pathways and binding repertoires.

[1] Pogenberg V, Ogmundsdóttir MH, Bergsteinsdóttir K, Schepsky A, Phung B, Deineko V, Milewski M, Steingrímsson E, Wilmanns M. Restricted leucine zipper dimerization and specificity of DNA recognition of the melanocyte master regulator MITF. Genes Dev. 2012 Dec 1;26(23):2647-58.

Keywords: basic zipper transcription factor; DNA-mediated protein dimerization; structure-based protein engineering