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DNA binding and dimerization specificities of Basic Zipper transcription factors

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The ability of basic zipper transcription factors to form homo- or heterodimers provides a paradigm for combinatorial control of eukaryotic gene expression. In a first study, we clarified the specificity of the MIcrophthalmia-associated Transcription Factor [1]. To achieve this, we solved three crystal structures: two structures of MITF in complex with DNA duplexes encompassing two different target motifs (E-box and M-box) and one APO-structure. We then analyzed interactions between these DNA elements and several MITF mutants with documented mice phenotypes, using complementary techniques. The comparison of these experiments together with available biological data reveals the particular mechanism of DNA recognition by MITF. Moreover we demonstrated how a shift in the leucine zipper register limits the choice of the homotypic dimerization partner among the other b-HLH-Zip transcription factors. In a second study, we wondered how facultative dimerization results in alternative DNA-binding repertoires on distinct regulatory elements [2]. In this respect, the hematopoietic b-Zip transcription factor MafB, is a good model, since it has the ability to form homo- and heterodimers with a few other transcription factors. 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 (MARE). The two structures revealed several unexpected and specific coiled coil interactions. Based on these findings, we have engineered two MafB mutants with opposite dimerization preferences. One of them indeed showed a strong preference for MafB/c-Fos heterodimerization. In addition this variant enabled a selection of heterodimer- favoring over homodimer-specific MARE 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] *V. Pogenberg, MH. Ogmundsdóttir, K. Bergsteinsdóttir et al, Genes & Development. 2012, 26(23):2647-58.,* ***[2]*** *V. Pogenberg, L. Consani Textor, L. Vanhille et al, Structure. 2014, In Press at the day of submission of this abstract.*

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