Chemical synthesis of c-Myc transactivation domain using a synthesis/solubility tag

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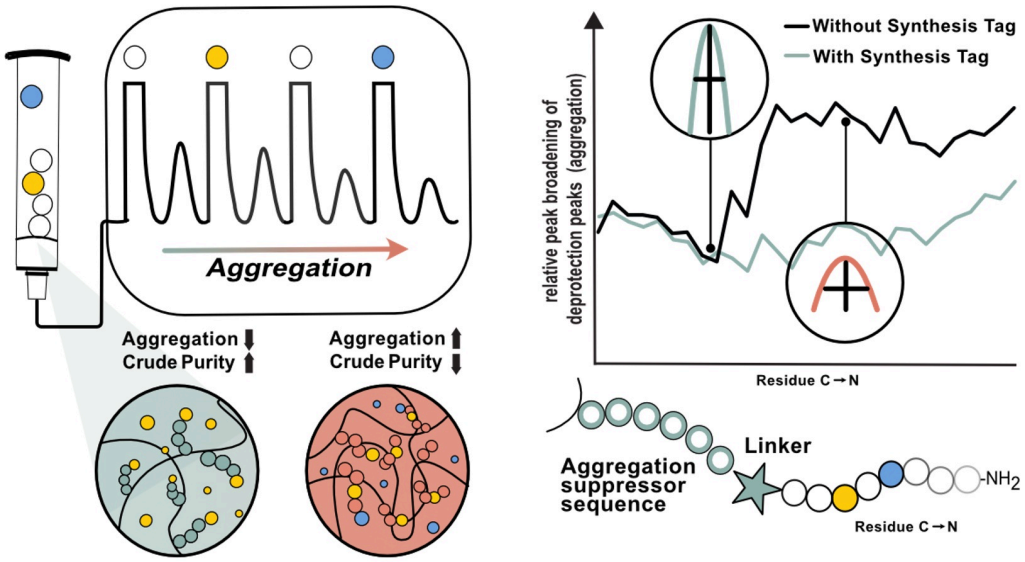
Chemical protein synthesis enabled by solid-phase peptide synthesis (SPPS) provides peptide and protein samples with a virtually unlimited chemical space (including PTMs) through incorporation of non-canonical amino acids and backbone modifications. Decades of improvement and optimization have increased the length of synthesized peptide chains of up to 50 amino acids.[1] Over this limit, Native Chemical Ligation (NCL) has been developed to join synthesized fragments, ultimately leading to the production of larger proteins.[2] Yet, generating fragments by SPPS in good yield and purity requires extensive synthesis efforts. A particular problem during the synthesis itself is the aggregation of the resin-bound peptides, which is highly sequence dependent. While several solutions have been developed to address the aggregation problem, identifying and suppressing its cause is still very challenging. A deeper understanding of aggregation, as well as a more general solution to this problem, are therefore urgently needed. Our flow-based fast peptide synthesizer (AFPS) with in-line UV analysis has the capacity to monitor aggregation during synthesis. Combining our results from screening various linkers and amino acid sequences resulted in the development of a versatile “synthesis tag”. The tag reduced aggregation for several “difficult peptides”, yielding significantly improved crude purities as well as enhanced peptide solubilities. As an application of the method, we now use our “synthesis tag” in the synthesis of the heavily aggregating transactivation domain (TAD) of the intrinsically disordered transcription factor MYC. [3]



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