Selective inhibition of biofilm-associated amyloids

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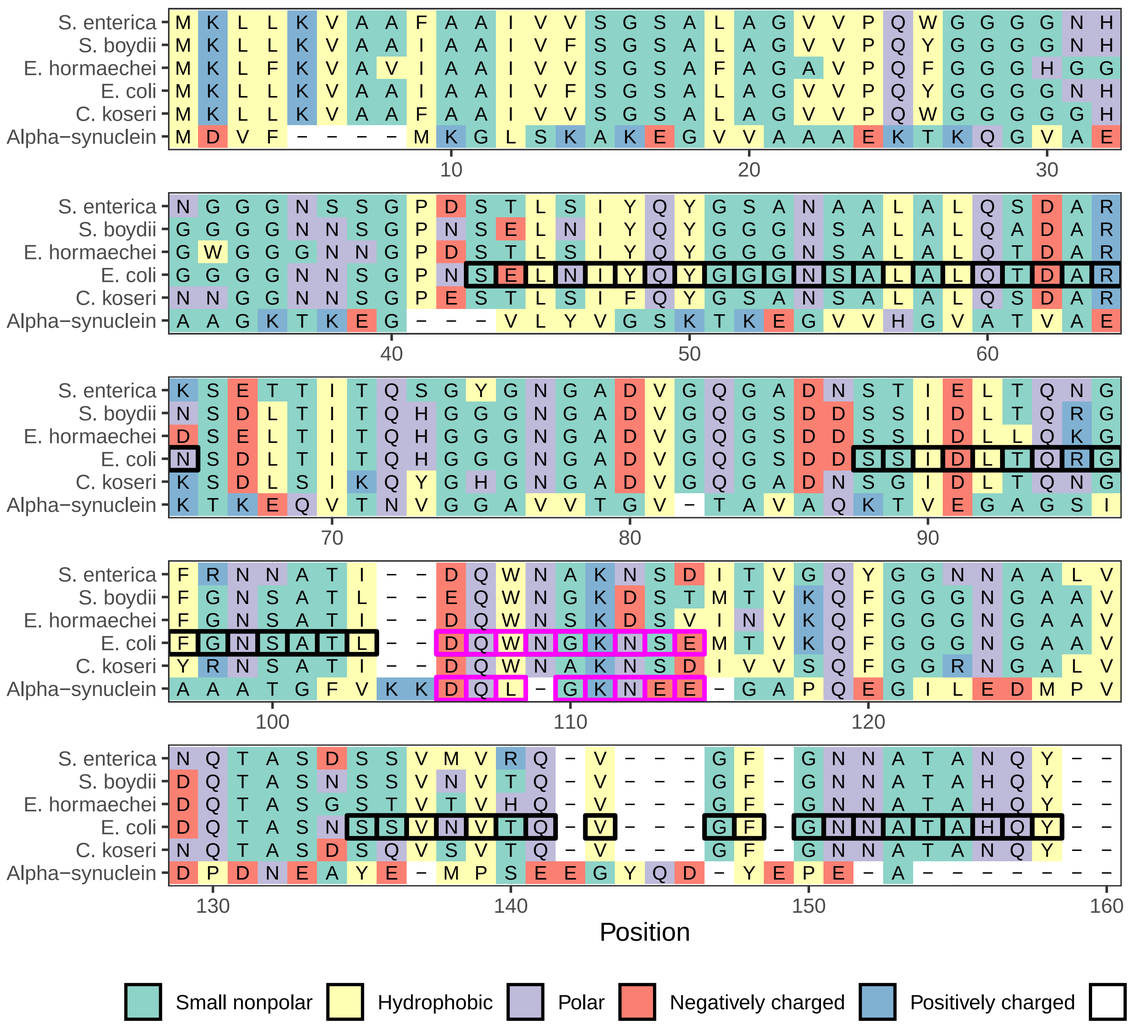
Introduction

Amyloid fibrils are heterogeneous proteins capable to self-assembly fibrous aggregates deposited in organs and tissues. These aggregates are associated with incurable degenerative illnesses such as Alzheimer's (amyloid β) and Parkinson's (α-synuclein) disease. Amyloid fibrils are made of soluble proteins, however, amyloid fibers are insoluble and resistant to degradation. The curli system that occurs in enteric bacteria consists of self-assembling functional amyloid, CsgA. Functional amyloids occur in natural environment in many biological system and, in contrast to amyloids associated with disorders, they are tightly controlled. For example, CsgA is effectively inhibited by CsgC [1]. In addition, CsgC inhibits human α-synuclein. CsgC possesses its functional homologues, such as CsgH [2] and transthyretin (TTR) [3], which also show antiamyloid activity despite completely different sequences. To check if there are significant differences among CsgA homologues and CsgC homologues, we carried out sequence comparisons. In addition, we compared CsgA and α-synuclein as well as CsgC with its functional homologues, CsgH and TTR.

Multiple sequence alignment of various species of CsgA and α-synuclein

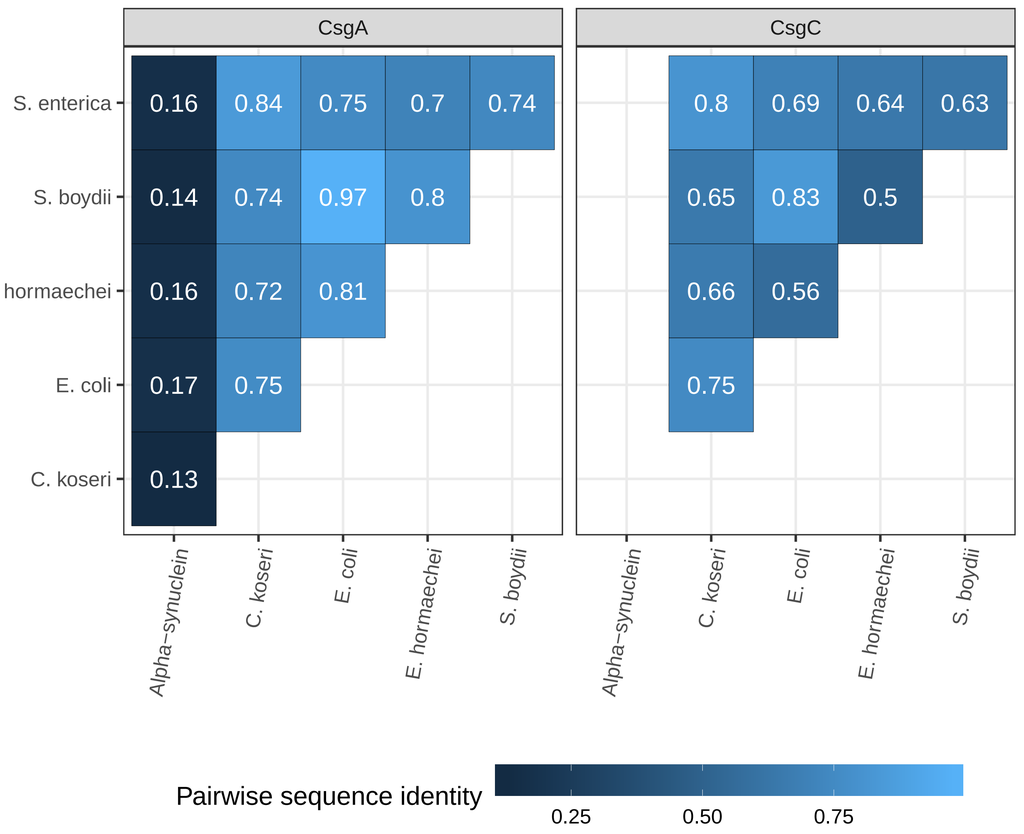


Repeated units from CsgA: R1, R3 and R5, are highlited on black. CsgAs and α-synuclein sequences shared only a single common region (highlighted in red), residues 104:112 in CsgA and residues 98:104 in α-synuclein. If the region is modified in α-synuclein, CsgC is unable to inhibit this protein.

Multiple sequence alignment of various species of CsgC

Motif CxC that is essential for the functioning of CsgC as an inhibitor is highlited on

Pairwise sequence identity of CsgA and CsgC



Significant homologues were found only in closely related bacteria. Generally, CsgA and CsgC showed very similar pairwise sequence identity in corresponding pairs of bacteria with the exception of CsgC from *Enterobacter hormaechei* which demonstrated much lower identity compared with other species.

Multiple sequence alignment of CsgC functional homologues

Motif CxC is highlited on black in CsgC. The alignment of curli inhibitors (CsgC, CsgH and TTR) showed no sequence similarity. The CxC motif, present in CsgC sequence and important in the inhibition of CsgA aggregation, does not exist in TTR and CsgH.

Conclusions

CsgC and CsgA sequences exhibit similar level of sequence divergence in their homologues except for one species. Nevertheless, functional homologues of CsgC, CsgH and TTR show no sequence similarity between them. Knowing that all these proteins are able to inhibit CsgA, we can assume that inhibitory properties are not manifested in the primary sequence and must depend on three-dimensional structure.

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