Solution Structure of Proline-Arginine Dipeptide Repeats Studied by Small-Angle X-Ray Scattering and Molecular Structural Simulation

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Segments of abnormal dipeptide repeats are often found in the gene chromosome 9 open reading frame 72 (C9ORF72) in the patients of familial frontotemporal dementia (a progressive disorder of the brain) and amyotrophic lateral sclerosis (muscles decreasing in size, resulting in difficulty in speaking, swallowing, and eventually breathing), as a signature of the deseases. Such dipeptide repeating of 10 – 1000 times can be found in the brain or spinal cord of the patients, including poly Glycine-Arginine $(GR)_n$, poly Glycine-Alanine $(GA)_n$, poly Glycine-Proline $(GP)_n$, poly Proline-Arginine $(PR)_n$, and poly Proline-Alanine $(PA)_n$. Current research shows that both GR and PR are cytotoxic. Especially PR is more cytotoxic than GR in Drosophila-eye experiement. To reveal structural insights of the repeating length of the dipeptide repeats (DPRs) on the development of the disease symptons, we have synthesized $(PR)_{30}$ and $(PR)_{10}$, and probe their solutions strucutres by integrative analysis of small-angle X-ray scattering (SAXS) and molecular structural simulation. The result indicates that $(PR)_{30}$ form a long helix in solution. The repeated-length dependent strucutres of $(PR)_n$ wil be discussed.