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GRAPHICAL ABSTRACT

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- Diagram illustrating the structural changes in the PHE and PHO proteins upon ligand binding. The top part shows a ribbon diagram of the protein structure with a red arrow indicating a conformational change. Below, four panels show the binding site residues (F, A, L, G, S, N) in different states: APHE, APHO, PHE, and PHO.

ABSTRACT

Polymorphic structures

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Pathological amyloid diseases are associated with several degenerative and neuro-degenerative diseases, such as senile heart disease, type II diabetes, Alzheimer's disease, and Huntington's disease [1,2]. The

origins of these diseases are the amyloid proteins developed by denatured and misfolded proteins [3,4], which disrupt and reduce the normal function of cells or proteins in the human body. Amyloid proteins such as tau, HET-s, human islet amyloid polypeptides (hIAPP), A β , β 2-microglobulin, and β 2-lactoglobulin fibrils exhibit various forms, such as 1D structures (i.e. nanotube and fibrillar structures) and 2D structures (i.e. films and angled layer structures) with hierarchical compositions of β strands [5]. The existence of amyloid fibrils in these forms can be referred to as polymorphism along with the various compositions and directions of β strands [6–8]. Furthermore, the thickness variation of amyloid fibrils as well as the number of protofibril structure were observed [9]. These amyloid proteins share cross β structures sustained with steric zipper interaction that renders them difficult to degrade in physiological environments [10–13]. Thus, understanding the stability of amyloid proteins has been recognized as a crucial step in elucidating the mechanisms of degenerative and neuro-degenerative diseases and providing treatment for these diseases.

However, the focus of research on amyloid fibrils has shifted from the role of the fibrils as a source of pathological diseases to their use as functional biological materials for conductive materials, nanosensors, bacterial biofilms, and coatings [14–16]. Amyloid proteins themselves possess material stability and mechanical properties, which can be compared to nanomaterials and biological materials, which could be evaluated by using force spectroscopy methods (i.e. atomic force microscopy and optical tweezers) and computational methods (i.e. molecular dynamics simulation and elastic network model) [17]. Knowles et al. demonstrated the material properties and characteristics of various kinds of amyloid fibrils such as insulin, TTR (105–115) (transthyretin), β -lactoglobulin and α -lactalbumin via experimental and computation methods, for example, reaching up to ~ 10 GPa of elastic moduli [18]. The study revealed that the cause of different structures of amyloid fibrils is the varying numbers of hydrogen bonds, and the material properties and characteristics may also vary depending on the cross section of area. Buehler et al. predicted the elastic modulus and rigidity of amyloid fibrils via various computational methods [19]. For these reasons, the role of amyloid fibrils has been risen in their use as a template for functional materials.

Many research groups have already developed amyloid fibril templates for functional materials such as nanosensors and nanodevices. For instance, in terms of amyloid nanosensors, Li et al. developed a selective gas sensor at given environments using amyloid fibrils [20]. They used tau amyloid protein as the selective capturing tool for carbon dioxide under various ranges of temperature and pressure. For amyloid fibrils used as conductive materials, Scheibel et al. developed amyloid fibrils as a template for conductive materials using gold nanoparticles [21]. In a similar manner, Li et al. developed functional conductive materials with shape-memory characteristics using α -lactoglobulin amyloid fibrils with graphene nanosheets [22]. From their study, they sustained excellent conductive characteristics with advanced material properties by adding amyloid fibrils. Yalamanova et al. utilized amyloid fibrils as enhancers of retroviral transduction to increase gene transfer in mice models [23]. Furthermore, Perutz et al. suggested that specific sequences of amyloid fibrils could form water-filled nanotubes [24].

From the various functional studies concerning amyloid materials, amyloid fibrils have been developed and used as functional materials due to their excellent material properties such as high elastic moduli, bending rigidity and toughness. Therefore, understanding the properties and characteristics of amyloid fibrils is important for the development of functional material templates using amyloid materials with various characteristics. Buehler et al. revealed, using tensile loading simulations via the number of hydrogen bonds broken, that the wide range of material properties exhibited by amyloid fibrils, such as two stacked β -sheets fibrils, three β -helical fibrils, and mixed fibrils, depended on the cross-sectional area [25]. Yoon et al. examined the differences in the structural and mechanical properties of HET-s fibrils comparing left-handed and right-handed directions using NMA (normal mode

analysis) simulations [26]. They also found that the material responses and properties were related to the secondary structure composition of amyloid fibrils. Ndlovu et al. studied the material response of wild-type and mutated hIAPP fibrils using various types of SMD (steered molecular dynamics) simulations [27]. From their study, they found the role of the hydrophobic residues and the effect of mutation on the stability of hIAPP fibrils. In this regard, the study of amyloid as a template for functional materials in terms of their material properties and characteristics is needed.

In our previous studies, we showed the material properties and characteristics of polymorphic hIAPP fibrils, which were evaluated via different types of deformation modes such as soft bending, stiff bending, torsion, and axial, using eigenvalue problems with ENM (elastic network model) and MD simulations [28,29]. Moreover, recently we studied the different material behaviors of hIAPP fibrils using constant bending simulations [30,31]. From our study, we showed the brittleness and ductility of polymorphic hIAPP fibrils as well as their material properties, such as Young's modulus and fracture toughness. Recently, Ndlovu et al. revealed the mechanical responses of four types of polymorphic hIAPP fibrils using different modes of SMD simulations [32]. They addressed that the mechanical responses of polymorphic hIAPP fibrils depended on structural composition. However, it is still challenging for the material property characterization of hIAPP fibrils using tensile loading simulations.

In the current study, we examined the material characteristics of the four kinds of polymorphic hIAPP fibrils using tensile SMD simulations. We observed that the elastic properties in the diverse polymorphs of hIAPP fibrils depended on the parallel and antiparallel structural composition or homo and hetero structural composition. Moreover, we determined the fracture toughness values using the number of broken hydrogen bonds and revealed the material characteristics of hIAPP fibrils.

2. Material and methods

2.1. Construction of polymorphic hIAPP structures

Amyloid proteins, such as A β , tau, prions, and insulin, have polymorphic characteristics because of their different structures, orientation with respect to the β strands, and their parallel or antiparallel compositions, as reported by Sawaya et al. [6]. The hIAPP amyloid proteins used in this study had eight kinds of polymorphic characteristics depending on the orientation of the stacked β strands (i.e. parallel and antiparallel), facing sides of β strands (i.e. homo and hetero), and direction of β strands themselves (i.e. co-aligned and anti-aligned), as shown by Neilson et al. [8]. To investigate the relationship between structural compositions based on the organization of each β strand, we considered four basic kinds of polymorphic structures: antiparallel hetero (APHE), antiparallel homo (APHO), parallel hetero (PHE) and parallel homo (PHO) (see Fig. 1(a), (b), (c) and (d) respectively). To construct the computational models of the polymorphic hIAPP structures, we adopted information from the PDB (Protein Data Bank), where the protein has an ID of 2KIB. The sequence used in this study is NFGAILS from the full sequences of hIAPP fibrils. Based on existing geometric information, we stacked the cross β strands, which are 8.75 nm in length scale, 4.7 Å along the axis direction [33]. During the stacking process of the hIAPP structure, we stacked the polymorphic structures sustained with steric zipper interaction to avoid penetration of water molecules between facing two cross β strands. In this process, the intersheet interaction was sustained as dry interfaces and no water molecules between facing β strands were found, also shown in Esposito et al. [10].

2.2. Composing polymorphic hIAPP fibrils

To form helical fibrillar shape of hIAPP fibrils from the stacked structures, we conducted equilibrated simulation on the polymorphic hIAPP

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