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The Cooperative Effect of both Molecular and Supramolecular Chirality on Cell Adhesion

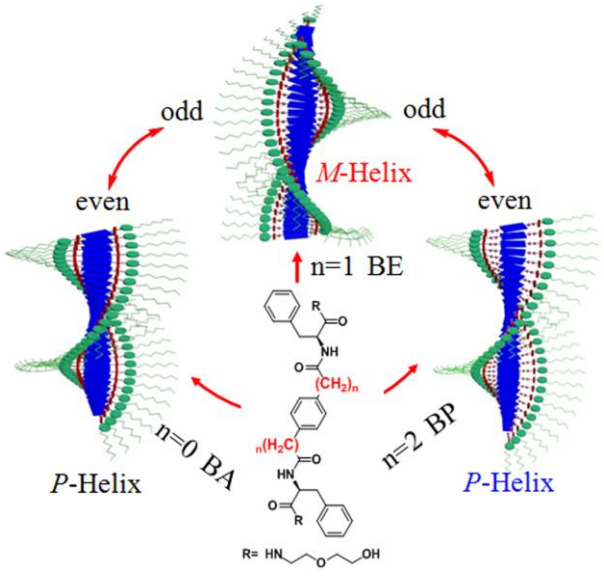
Jinying Liu,[a] Feng Yuan,[a] Xiaoyu Ma,[a] Dang-i Y. Auphedeous,[a] Changli Zhao,[a] Chuntai Liu,[b] Changyu Shen[b] and Chuanliang Feng*[a]

Dedication ((optional))

Abstract: Although helical nanofibrous structures have great influence on cell adhesion, the role played by chiral molecules in these structures on cells behavior is usually ignored and still unclear. In this paper, the chirality of helical nanofibers is inverted by odd−even effect of methylene units from homochiral *L*-phenylalanine derivative during assembly. An increase in cell adhesion on left-handed nanofibers and weak influence of cell behaviors on right-handed nanofibers are observed, even though both were derived from *L*-phenylalanine derivatives. Weak and negative influences on cell behaviour was also observed for left and right handed nanofibers derived from *D*-phenylalanine respectively. It is considered that the effect on cell adhesion of single chiral molecules and helical nanofibers may be mutually offset. This study not only presents a viable strategy to achieve the handedness inversion of helical nanostructures by the odd-even effect, but also provides a method to touch the fundamental problems for the studies in the origins of life and the high chiral preference of life.

Helical architectures (e.g., DNA or proteins) are present in many biomolecular systems, where they occasionally perform helicity inversion in many physiological processes along with specific biofunctional transformations.[1] Pioneering researches reveal that the handedness of nanoarchitectures not only have a profound effect on stem cell differentiation, cell adhesion and protein adhesion,[2] but also applicatications in areas of sensing or recognition,[3] catalysis,[4] chiroptical switches,[5] and medicine.[6] Although the helical chirality of nanoscale architectures is significant in biomaterial and relevant biological studies, these helical assemblies are usually fabricated with enantiomeric building blocks, and the enantiomeric effect of the single molecule cannot be shielded when searching for their biological functions.[2b,c] This ascribes to the property of the molecular chirality which can be kept or amplified upon forming these helical assemblies, besides single chiral molecule usually reveals opposite influence in many biological events depending on their chirality.[7] In view of the basic building blocks of biomacromolecules fabricated with homochiral small molecules, such as *L*-amino acids (except glycine) and *D*-saccharides, controllable helical supramolecular assemblies constructed with enantiomers are averse to mimic helical inversion events of these biomacromolecules and elucidate their specific bio-functional transformation.

To address this issue, it is helpful to use only one enantiomer to construct supramolecular architectures with controlled helical chirality and favorable biocompatibility, where handedness inversion of the self-assemblies would be triggered by achiral factors. Although many chirality inversions of supramolecular assemblies have been mediated by achiral factors, such as a change in solvent[8] or temperature,[9] light irradiation,[5a, 10] slight structural change,[11] addition of chemical species[12] and rotary stirring,[13] these existing helical inversion of supramolecular nanostructures are still far behind biomolecular systems in terms of biocompatibility and functionality. It is known that the odd-even effect could successively change a property just through varying the position or number of a structural element from an odd number or an even number. Recently, the ability to change gels and the morphology of supramolecular structures with the odd-even effect has been reported,[14] however, using odd-even effect to tune the handedness of supramolecular nanostructures transitioning them between *P* and *M* is rarely reported.[15]



Scheme 1. Chemical structure of BA, BE and BP, and schematic illustration of helical chirality inversion tuned by the variable methylene units.

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Herein, chirality regulation of hydrogels self-assembled from C_2-symmetric hydrogelators through odd−even effect of methylene units are studied (n=0, 1, 2). The chirality of the assembled nanofiber depends on n, which can form right-handed (*P*-type) nanofibers if methylene number is even (n=0, BA; n=2, BP) and left-handed (*M*-type) nanofibers if it is odd (n=1, BE) (Scheme 1). Mouse embryonic fibroblast cell line (NIH 3T3) and human-derived EA.hy926 endothelial cells (Hy926) were used to investigate cell adhesion and proliferation on two-dimension (2D) films. The cell densities of fibroblast cells and endothelial cells on BE film are 1.2-folds and 1.3-folds as high as those on BA and BP film, respectively. The results show an increase in cell adhesion and proliferation with left-handed nanofibers, whereas right-handed nanofibers have weak influence, even though these nanofibers are all assembled from *L*-phenylalanine derivatives. The result suggests that the effect on cell adhesion of single chiral molecules and helical nanofibers may be mutually offset. This finding provides novel insight into touching the fundamental problems for the studies in the origins of life and the high chiral preference of life.

The syntheses of BA, BE and BP are outlined in Supporting Information (Scheme S1-S3), similar to previously published strategies. All the newly reported compounds have been fully characterized by NMR and high-resolution mass spectrometry (Supporting Information). The ability of compounds BA, BE and BP to self-assemble into hydrogels was tested in distilled water (milli Q). The hydrogel formation was judged by the "invert-vial" method (Figure S1), and the rheological properties of hydrogels were measured using a rotary rheometer with dynamic frequency sweep at a strain of 0.01%. The higher values of elastic modulus (*G'*) than those of viscous modulus values (*G''*) further indicated the formation of solid gels (Figure S3).

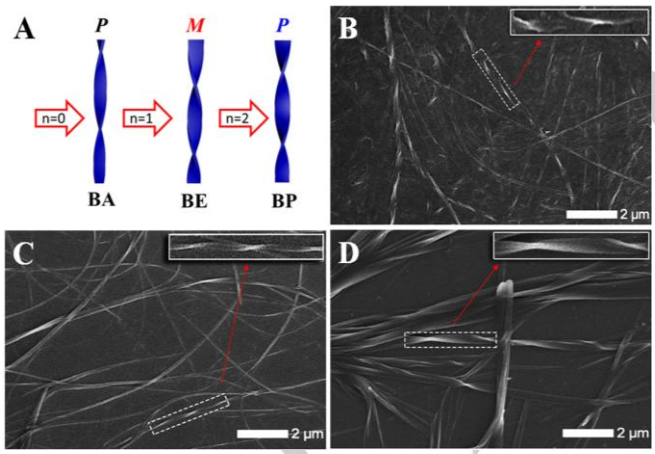


Figure 1. A) Schematic illustration of twisted nanofiber BA、 BE and BP, *M* and *P* denote left- and right-handed helical or twisted nanofibers, respectively. B) SEM images of right-handed helical fibers in the BA xerogel, C) SEM images of left-handed helical fibers in the BE xerogel, D) SEM images of right-handed helical fibers in the BP xerogel.

To investigate the morphology of nanostructures self-assembled from BA, BE and BP, SEM images were employed. BA and BP with an even number of methylene units (n=0, 2) produced right-handed twisted nanofibers. The diameter and helical pitch of BA nanofibers are ~80 nm and ~1.5 μm (Figure 1B), ~310 nm and ~2.2 μm for BP (Figure 1D), respectively. However, well-defined left-handed twisted nanofibers with the diameter of 155 nm and helical pitch of 1.6 μm were observed for BE nanofibers (Figure 1C). Here, all the hydrogelators possess the same *S*-type stereo center within the peripheral *L*-phenylalanine units, thus, the chiral inversion was obviously triggered by methylene numbers and the variable methylene units slightly alter the conformation of the disk in the stack, inducing a small change in the pitch and diameter of the helix. Left-handed and right-handed nanofibers of the *D*-enantiomer of BA and BE were also observed from the SEM images respectively (Figure S 13 c and d).

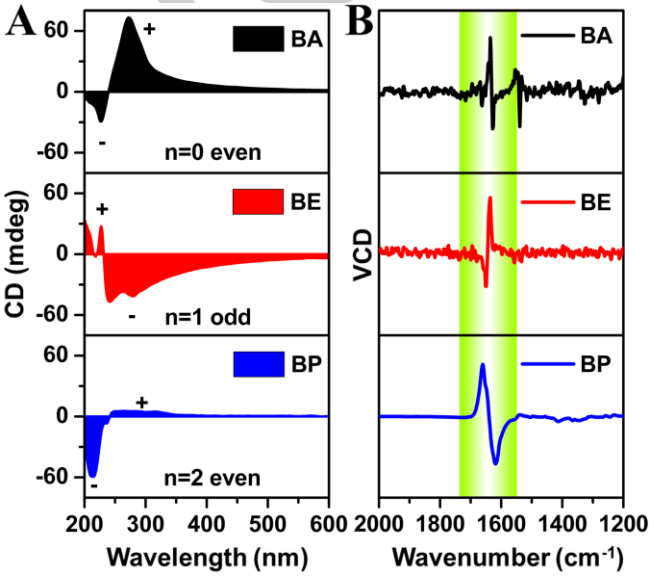


Figure 2. A) CD spectra of the BA, BE and BP, hydrogels were obtained by using a 0.1 mm quartz cuvette with a total gelator concentration of 2.0 mg/mL BA, 3.0 mg/mL BE and 9.0 mg/mL BP (with 3% DMSO in water), B) VCD spectra of the BA, BE and BP xerogel.

The helicity of the aggregates formed by BA, BE and BP in gel state was investigated by CD spectroscopy at room temperature (Figure 2A). The CD spectrum of BA (Figure 2A top) in water shows significant Cotton effect with an isodichroic point, zero crossing at 239 nm, and a strong positive (273 nm) and weak negative (228 nm) CD signals. Similarly, weak positive Cotton effects (273 nm) and strong negative CD signals (215 nm) were observed for BP (Figure 2A bottom). However, as expected, the Cotton effect of BE is opposite in sign compared with BA and BP. The CD spectra of the BE (Figure 2A middle) clearly showed the bisignated Cotton effect with a positive maximum at 227 nm and a negative maximum at 240 nm. The CD signal of BA, BE and BP showed a clear sign inversion with odd-even number methylene units placed between the chiral center and benzene group, which is in good agreement with SEM results. It must be pointed out that the structure of BA, BE and BP have slight change, so their CD spectra should not be exact mirror images. CD spectra for the *D*-enantiomer of BA and BE further confirmed

the chirality inversion caused by the number change in methylene units (Figure S 13 b).

The chiroptical activities of these hydrogels were also investigated by vibrational circular dichroism (VCD, Figure 2B). BA (Figure 2B top) and BP (Figure 2B bottom) exhibited a same (-/+) signal of C=O stretching band between 1750 and 1600 cm^{-1}, conversely the VCD signal of BE showed a significant (+/-) pattern between 1700 and 1600 cm^{-1} (Figure 2B middle). Hence, a strong and extensive C=O•••HN hydrogen-bonding network, significantly stabilizing the supramolecular hydrogels of BA, BE and BP, is inferred from the vibrational amide I stretching band at around 1636 cm^{-1}. The VCD patterns imply the inversion of the chirality from BA to BE to BP, which may be ascribed to the different number of methylene units. This is in congruence with SEM and CD experiments, which show that BA have right-handed nanofibers, BE, left-handed nanofibers and BP, right-handed nanofibers.

In the view that surface wettability of the xerogels has a great influence on cell adhesion and protein adsorption,the surface hydrophilic properties of the xerogels membrane of BA、BE and BP were characterized by contact angles (Figure S4), 38.3°± 2.9° for BA, 45.5°±3.7° for BE and 46.5°±3.4° for BP, indicating a similarity in wettability. This is ascribed to the peripheral group with uniform hydrophilic 2-(2-Aminoethoxy)ethanol for the three gelators.

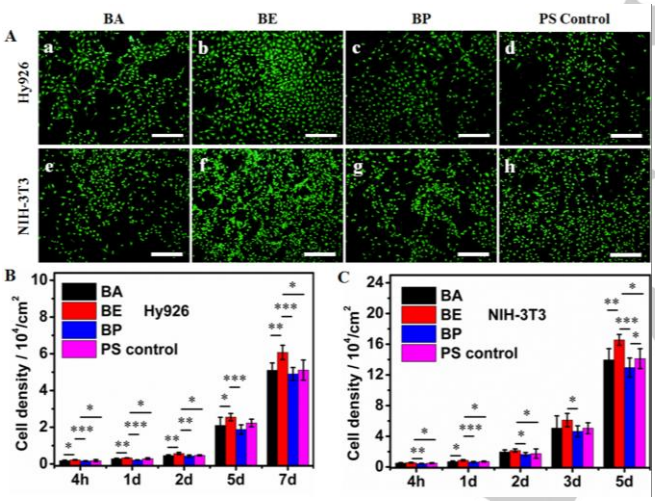
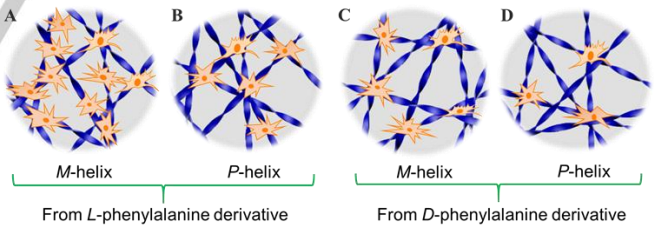


Figure 3. A) Fluorescence microscopy images of Hy926 cells after culture for 5 days (a, b, c and d) and NIH 3T3 cells after culture for 3 days (e, f, g and h) on BA, BE, and BP nanofiber films and PS Control well. Scale bar: 100 μm. B,C) Quantitative data for Hy926 cells (B) and NIH 3T3 cells (C) on BA, BE, and BP nanofiber films and PS Control well after incubation for 4 h, 1 day, 2 days, 3 days, 5 days, and 7 days. N=6; *, **, *** data show significant differences (ANOVA: *p0.05, ** p0.005, *** p0.001).

To assess the effect of chiral nanofibers arising from BA、BE and BP on cell-adhesion and cell-proliferation behavior, mouse embryonic fibroblasts NIH 3T3 cells were seeded (ca. 2000 cells per well) on a two dimensional (2D) substrate coated with BA, BE, and BP nanofiber films, and the polystyrene (PS) well was used as control. The cells were incubated at 37 °C and 5% CO_2 for 4 hours, 1 day, 2 days, 3 days, and 5 days. After incubation for 4 h, the quantity of adhered live cells on the BE films was 1.2 times and 1.3 times as high as that on the BA films and BP films, respectively (Table S2), and showed well spreading morphology, which indicated good cell adhesion. While cell number on the BA and BP films was not statistically different compared with the controlled PS plate (Figure S8). At the next four time points, cell growth density was found to be proportional to the original adhesion density for each film (Figure 3 and Figures S8), indicating better cell adhesion is the critical prerequisite for gaining higher cell proliferation. The good cytocompatibility of the nanofibers was also proved by a live–dead staining assay (see Figure S7). To further confirm the chirality effect of the nanofiber on different cell type, endothelial cells Hy926 were plated on the different films (ca. 2000 cells per well). The results were similar to those observed on the NIH 3T3 cells, i.e. both the cell-adhesion and cell-proliferation density on BE films was about 1.2 times as high as that on the BA films and about 1.3 times as high as that on BP films (Table S3 and Figures S10 and S11). These results demonstrated left-handed helical nanofibers can increase cell adhesion and proliferation whiles right-handed nanofibers had weak influence, even though both nanofibers were derived from *L*-phenylalanine derivatives. Also, the stereospecific interaction between the cells and these chiral nanofibers is a common effect that can be applied to different cell types. We went ahead to confirm the effect of molecular and supramolecular chirality on cell adhesion and proliferation by seeding the mouse embryonic fibroblasts NIH 3T3 (ca. 2000 cells per well) on the *D*-enantiomer of BA and BE (*d*-BA and *d*-BE respectively). The results showed a weak influence on cell behavior by left-handed nanofibers from *D*- phenylalanine (*d*-BA) and a negative influence on cell behavior by right-handed nanofibers from *D*- phenylalanine (*d*-BE) (Figure S14, S15 and Table S4).



Scheme 2. A) Positive effect on cell adhesion on left-handed nanofibers derived from *L*-phenylalanine derivative; B, C) Weak effect on cell adhesion on right-handed nanofibers derived from *L*-phenylalanine derivative and left-handed nanofibers derived from *D*-phenylalanine derivative; D) Negative effect on cell adhesion on right-handed nanofibers derived from *D*-phenylalanine derivative.

Our previous work has proved that left-handed helical nanofibers self-assembled from *L*-phenylalanine derivative have positive effect on fibroblast and endothelial cell adhesion. On the contrary, the right-handed nanofibers derived from *D*-phenylalanine derivative induced a decrease in cell adhesion density (Scheme 2A, 2D).[2c] It ascribes to the kept or amplified property of *D*-enantiomer chirality upon forming helical assemblies, while, it proves that *D*-enantiomer modified surfaces

are not favorable for cell adhesion compared with *L*-enantiomer surfaces.[7a,7c,7f] Herein, *L*-phenylalanine chiral property should also be kept in the right-handed helical nanofibers derived from *L*-phenylalanine derivatives. Although cells prefer to interact with *L*-enantiomer molecules, the right-handed nanofibers have opposite influence on cell adhesion. This mutual offsetting leads to the weak influence on cell adhesion on the right-handed BA and BP nanofibers (Scheme 2B). In a similar manner, left handed nanofibers from the *D*-enantiomer molecule *d*-BA displayed a weak influence on cell adhesion (Scheme 2C, Figure S14-15 and Table S4). Thus, it is considered that the design of helical nanofibers with homochiral small molecules (e.g., *L*-amino acids, *D*-saccharides) may bring a novel direction for biomaterial design, which is helpful to touch the fundamental problems for the studies in the origins of life and the high chiral preference of life.

In conclusion, the helicity inversion of supramolecular assemblies based on C_2 symmetric *L*-phenylalanine derivatives has been successfully achieved through inserting variable methylene units between the chiral center and rigid aromatic core. It shows an increase in cell adhesion and proliferation on left-handed nanofibers and weak influence on cells behaviors on the right-handed nanofibers, though both types of helical nanofibers are derived from *L*-phenylalanine derivatives. The results provide some initial design rules for constructing helical supramolecular architechture with homochiral small molecules through the odd-even effect. Typically, this tunable helical chirality system also paves a new way to assess the bio-effects of right- and left-handed helical supramolecular assemblies by circumventing enantiomeric effect of single molecules.

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Keywords: Odd-even effect • Chirality inversion • Methylene unit • Cell adhesion • supramolecular chemistry

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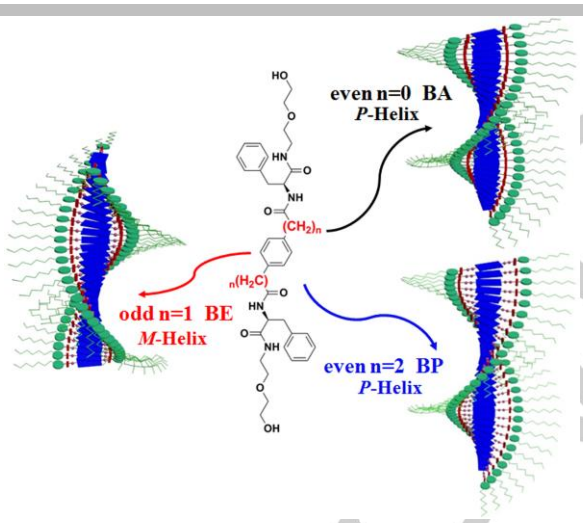
Layout 1:

COMMUNICATION

The chirality inversion of helical nanofibers is triggered by odd−even effect of methylene units from homochiral *L*-phenylalanine derivative during assembly. The results show an increase in cell adhesion and proliferation with left-handed nanofibers whereas weak influence was observed with right-handed nanofibers, even though both were derived from *L*-phenylalanine derivatives.



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The Cooperative Effect of both Molecular and Supramolecular Chirality on Cell Adhesion