Biomolecular Piezoelectric Materials: From Amino Acids to Living Tissues

Daeyeong Kim, Sang A Han, Jung Ho Kim, Ju-Hyuck Lee,* Sang-Woo Kim,* and Seung-Wuk Lee*

1. Introduction

The phenomenon of the conversion of mechanical energy into electrical energy is termed piezoelectricity. Applying mechanical energy to piezoelectric material deforms its crystal structure, and generates an electrical moment (i.e., called direct piezoelectric effect), and vice versa (i.e., called inverse piezoelectric effect). The polarization charge density induced by the electrical moment is proportional to the mechanical stress applied.[1–4] It is known that piezoelectricity is generated only in crystals without inversion symmetry. Most interestingly, piezoelectricity has been found in many organs made of biological materials that make up the human body or nature, such as bone, tendon, skin, hair, wood, clamshell, virus, protein, amino acid, deoxyribonucleic acid (DNA), nucleotides, and tymine (Figure 1a).[5–20]

That is, the structure of these organs is piezoelectric structure without inversion symmetry or they are composed of a piezoelectric material. For example, organs such as bone, cartilage, ligament, tendon, skin, and hair are composed of collagen or keratin, which are piezoelectric proteins, while wood is composed of cellulose, which is known as piezoelectric material.[5,9,14,17,21–24]

In particular, bone is composed of collagen and hydroxyapatite ceramics. Early research suggests that the piezoelectricity of bone originates from collagen, a nonsymmetrical structured protein, rather than hydroxyapatite, a centrally symmetric structured ceramic.[25,26] However, more recent studies suggest that hydroxyapatite may also have piezoelectricity.[27–29] The origin of these traits and the role of piezoelectricity in nature, especially in human body, are not yet fully understood, but are believed to be closely related to the health condition. For example, in the case of bone, mechanical stress on the bone produces electrical signals that are known to promote bone growth, healing, and remodeling.[30–33] Stress acting on the bone creates an electric potential, and attracts osteogenic cells due to the formation of electric dipoles. It subsequently accumulates minerals, mainly calcium, on the compression side of the bones.[22,34–37] Therefore, it is hypothesized that the piezoelectric effect increases bone density. This was discovered in 1892 when Julius Wolff observed that bone changed shape in response to the force acting on it, a phenomenon known as Wolff’s law (Figure 1b).[38–40] This law explains that the density of bones depends on the change in force acting on the bones.[41–44] Changes in the shape and the functionalities of the bone can be understood from the observation of change of the internal structure and shape of the bones.[39,45] Thus, in mature bones with common shapes, the elements of the bones...
respond to the mechanical demands imposed upon them by placing themselves, moving, and reducing or increasing their mass. This theory is supported by observations that bones are atrophied when mechanically unstressed and hypertrophied when stressed. Thus, the piezoelectric effect occurring in bone was found to play an important role in the development of bone structure and the mechanical delivery of bone at the cellular level. In addition, the effects of electrical stimulation on bone healing were examined in vitro and in vivo, and application of these stimuli proved to be capable of enhancing and stimulating osteogenic activity.\(^{44,46–50}\) In this way, osteocytes protect bone tissue with electromechanical signals and are affected by the piezoelectric properties of the bone, so mechanical stimulation is naturally converted into electrical stimulation. These cell development and regeneration effects are expected to apply to other connective tissues, such as ligament, cartilage, tendon, skin, hair, outer hair cells, cornea, and sclera.\(^{51}\) Therefore, it is important to understand the origin of these traits and the role of piezoelectricity in the human body, because they would be closely related to human health. In order to understand the origin of piezoelectricity in biological tissues and complex organs, it is important to understand the basic principles of conventional piezoelectric materials such as inorganic and organic materials, as well as to understand the piezoelectric properties of amino acids, peptides, and proteins, which are the basic building blocks of our tissue matrices (Figure 1c). In this review, we comprehensively discuss the piezoelectric properties of amino acids, peptides, proteins, and biological tissues, from the biological basic building blocks to the resultant complex tissue structures.

2. Piezoelectricity of Amino Acids

Amino acids are basic building blocks for proteins (i.e., collagen, keratin, etc.), and they exhibit structure-dependent piezoelectric properties.\(^ {52,53}\) An amino acid is an organic compound containing a carboxyl (\(-\text{COOH}\)) group, an amine (\(\text{NH}_2\)) group, hydrogen, and a side functional group, \(R\) that is specific to each amino acid. When \(R=H\), glycine is the simplest structure of amino acids. Amino acids are capable of forming 3D crystal structure, and if the crystal of the amino acid belongs to the so-called 20 piezoelectric crystal classes, can exhibit piezoelectric properties, like other crystals.\(^ {54}\) In 1970, Vasilyev et al. investigated the piezoelectricity in various amino acids.\(^ {55}\) They analyzed the piezoelectric property of amino acids crystals of different structures, such as left-handed (l), right-handed (d), and dl structures (dl amino acids contain both l- and d-amino acids and are termed racemic mixtures) using nuclear quadrupole resonance spectrometer, and compared with theoretical predictions. Figure 2a shows the schematics of the chemical structures of the representative chiral amino acids of l-alanine and d-alanine. The most of the experimental piezoelectric characterization results are in good agreement with the theoretical properties that correspond to the crystallographic classes discovered, except for the crystal structure of some unidentified amino acids.\(^ {56}\) In 2000, Lemanov et al. also grew a large number of single-crystal amino acids and their compounds using the aqueous solution method, and characterized their piezoelectric response using nuclear quadrupole resonance spectroscopy.\(^ {56}\) Furthermore, the temperature dependence of the piezoelectric response was also investigated.\(^ {56,57}\) The change in piezoelectric characteristics of amino acids with temperature change is due to phase transition and attenuation of the elastic vibration in the crystal, which is similar to the behavior of conventional piezoelectric crystals. Most amino acids exist in a chiral
Figure 1. Piezoelectric effect of biological materials and its hierarchical structure. a) Piezoelectricity of tissues in the human body. b) Piezoelectricity on bone for the cell regeneration. c) Hierarchical structure of piezoelectric bone consisting of piezoelectric collagen, peptide, and amino acids.

Figure 2. Piezoelectricity of amino acids. a) The chiral enantiomers of alanine with mirror plane. The left-handed L-alanine is presented with its mirror image, the right-handed D-alanine. b) Schematic of the longitudinal piezoelectricity in polycrystalline L-amino acids films. Reproduced with permission. Copyright 2018, American Chemical Society. c) Crystal packing controls the orientation of alanine molecular dipoles (green arrows) in the unit cell, which determines the magnitude and direction of the corresponding piezoelectric responses. Reproduced with permission. Copyright 2019, American Physical Society.
symmetric group, l or d form, and thus exhibit a piezoelectric response. Generally these chiral symmetric group crystals allow shear piezoelectric tensors, $d_{14}$, $d_{35}$, and $d_{56}$, but no longitudinal piezoelectric tensors such as $d_{11}$, $d_{33}$, and $d_{15}$.[55–63] However, the longitudinal piezoelectric tensor in piezoelectric materials is significantly important, and has great advantages for practical piezoelectric applications, because most of the environmentally available types of mechanical forces are of compressive or tensile direction. Very recently, theoretical and experimental studies of the longitudinal piezoelectricity of chiral amino acid crystal films have been reported. In 2018, Guerin et al. reported that the crystalline film of orthorhombic l-amino acids prepared by drop-casting method exhibited strong longitudinal piezoelectricity (Figure 2b).[62] The presence of longitudinal piezoelectricity in the l-amino acid film was well matched with density functional theory (DFT) calculations, and it was also found that there is a spontaneous polarization in the axial direction that could exhibit pyroelectric properties. In addition, they also in 2019 investigated the piezoelectricity of the racemic amino acid dl-alanine.[63] Since the sum of the dipole vectors in l-alanine is zero, there is no net polarization in the unit cell and no longitudinal piezoelectricity occurs. In contrast, dl-alanine has longitudinal piezoelectric properties, since the dipole vectors all point in the same direction (Figure 2c). Crystal films of dl-alanine were grown and piezoelectric properties were measured using DFT-guided experiments. The measured longitudinal piezoelectric coefficient of dl-alanine films showed maximum 4.8 pC N$^{-1}$, and an open-circuit voltage of 0.8 V was produced from dl-alanine films grown on a copper electrode based energy generator under manual compression.

Glycine, the only nonchiral amino acid, is known to crystallize into three different polymorphs, α, β, and γ-glycine.[64–67] The crystal class of α-glycine is a central symmetry point group, which excludes piezoelectricity. On the other hand, the crystal classes of β-glycine and γ-glycine must exhibit piezoelectric reaction, because they have a noncentral symmetry point group (Figure 3).[58–72] Initial studies of glycine reported very low piezoelectric coefficients, and its origin remained unclear. However, recent studies have shown that glycine exhibits very strong piezoelectric properties, and have investigated the origin of the piezoelectric response of β and γ-glycine using DFT simulations.[73] In 2018, Guerin et al. reported that through computational and experimental results, both β and γ-glycine show considerable piezoelectric responses. The most noteworthy of the results is that the piezoelectric coefficient $d_{16}$ predicted in β-glycine reaches about 200 pm V$^{-1}$, and this has also been confirmed experimentally (Figure 4a).[71] This high value of piezoelectric coefficients is comparable to or better than that of the conventional piezoelectric inorganic or organic materials. In addition, the piezoelectric device based on γ-glycine crystals sandwiched between electrodes was fabricated, and produced open-circuit voltage of 0.45 V by application of 0.172 N force. In order to apply the piezoelectric material to practical applications such as sensor, optics, and energy, it is necessary to fabricate uniform and unidirectionally aligned polarization of the piezoelectric material. Most of the traditional piezoelectric materials such as lead zirconate titanate (PZT), barium titanate (BTO), and polyvinylidene fluoride (PVDF) exhibit ferroelectric behavior, which makes it possible to easily align the polarization direction by application of an external electric field, called the poling process. However, it has been known that polarization in a biological system is clearly defined by the structure, and is limited in being controlled by an external electric field. Therefore, various biomaterials exhibit piezoelectricity, but generally do not show ferroelectricity. Recently, β and γ-glycine crystals have also been found to exhibit ferroelectricity and it is therefore possible to control the polarization direction through an external electric field.[73,74] In 2012, Heredia et al. reported for the first time, that piezoelectric γ-glycine exhibits robust and continuous nanoscale ferroelectricity, and that in principle, ferroelectric behavior

![Crystalline class of glycine polymorphs](image)

Figure 3. Molecular dipole calculated for the piezoelectric response in glycine crystals. a) Molecular dipoles calculated (green arrows) from the centrosymmetric α-glycine do not exhibit piezoelectric properties. b) The sum of the molecular dipoles of β-glycine contributes to the longitudinal 22 piezoelectric coefficient, because spontaneous polarization appears in the Z-axis. c) Molecular dipoles contributing to high shear piezoelectricity in β-glycine. d) The sum of the dipoles of γ-glycine contributes to the longitudinal 33 piezoelectric coefficient, because it has spontaneous polarization along the 3-axis. e) A “top-down” view of the γ-glycine unit cell along the [001] crystallographic direction. Reproduced with permission.[71] Copyright 2018, Nature Publishing Group.
can be sustained at a single molecule level (Figure 4b). The switchable ferroelectric domains in microcrystals of gamma glycine from the solution were observed using local electromechanical measurement, and the experimental results were proved by molecular simulations. In 2015, Bystrov et al. simulated ferroelectricity on $\beta$ and $\gamma$-glycine crystals and concluded that $\beta$ glycine should be more easily switchable with better ferroelectric properties, compared to $\gamma$-glycine. In addition, in order to elucidate more deeply the ferroelectric behavior of glycine, including both the equilibrium polarizations and the dynamic phase transition mechanism, Hu et al., in 2019 performed first-principles DFT calculations and molecular dynamics (MD) simulations. They reported that polarizations for the two $\gamma$-glycine phases ($P_{31}$, $P_{32}$) are 70.9 and 70.7 $\mu$C cm$^{-2}$ along the c-axis which is about five times stronger than that of $\beta$-glycine (11.82 $\mu$C cm$^{-2}$ along the b-axis) and are similar to those for traditional ferroelectric materials (Figure 4c–e). The molecular volume of crystals is similar for both $\beta$ and $\gamma$-glycine. However, $\gamma$-glycine has stronger polarization than that of $\beta$-glycine because $\beta$-glycine has dipoles in different directions, but $\gamma$-glycine dipole is spirally aligned along the axis. These findings of strong piezoelectricity and ferroelectric properties in amino acid crystals will open up potential applications of energy generation, bioelectronics logic, optics, sensors, and memory devices.

### 3. Piezoelectricity of Peptide

Peptide is a molecule composed of amino acids, and exhibits structure-dependent piezoelectric properties. The chemical bond between two amino acids through the carboxyl group of one amino acid and the amine group of the other is called a peptide bond or an amide bond. Peptide that is composed of two amino acids linked by a single peptide bond is called dipeptide. With more addition of amino acids, we can call tripeptides, tetrapeptides, pentapeptide, and so forth. A long and unbranched amino acid chain is called a polypeptide.

The di-phenylalanine (FF), the dipeptides of two phenylalanine (F), is one of the most notable piezoelectric biomolecules. The FF dipeptide can self-assemble into well-ordered nano-microtubes by a hydrogen bonding and $\pi-\pi$ stacking to form a non-centrosymmetric hexagonal crystal structure ($C_{6h}$) that can exhibit piezoelectricity (Figure 5a). In 2010 by Kholkin et al., FF nano-microtubes were synthesized by a solution process and examined by piezoresponse force microscopy (PFM) technique for the first time. Strong shear piezoelectric responses, $d_{15}$ (35 pm V$^{-1}$ for 100 nm and 60 pm V$^{-1}$ for 200 nm in diameter), were detected in self-assembled FF nano-microtubes directed along the tube axis. In 2016, Vasilev et al. measured the piezoelectric coefficients $d_{33}$, $d_{31}$,
$d_{15}$ and $d_{14}$ of FF nano-microtubes using the PFM method, and reported the values of 18 ± 5, 4 ± 1, 80 ± 15, and 10 ± 1 pm V$^{-1}$, respectively.\cite{82} The measured piezoelectric coefficients of FF nanotubes show strong piezoelectric property comparable to conventional piezoelectric materials. However, very limited realization of piezoelectric device applications was achieved because of the difficulty of fabricating uniform and unidirectionally polarized FF nanotubes over a large area. Although ferroelectric-like behavior in orthorhombic FF tubes after heat treatment was reported, only partial polarization switching was observed by the application of a strong electric field, because of the high coercive field.\cite{95-98} Recently, the methods of aligning the polarization direction of self-assembled FFs structure were introduced. In 2016, Nguyen et al.

---

**Figure 5.** Electric-field-induced vertically polarized FF peptide nanotube piezoelectric properties. a) Schematics of the FF molecule (above) and formation of the molecular ring from 6FF molecules bound by the hydrogen bonds between FF molecules (below). b) Schematics of the vertical growth of FF peptide microrod array with controlled polarization by application of the electric field. c) Statistics of the piezoelectric phase for the arrays from the positive electric field (EF) growth, negative EF growth, and no EF growth. d) Linear dependence of the open-circuit output voltage from the piezoelectric generators on the applied force. Reproduced with permission.\cite{99} Copyright 2016, Nature Publishing Group.
reported a method for controlling the polarization of FF tubes by the application of an electric field during the peptide self-assembly process.\(^9\) The FF seed film was first formed on the substrate, and vertically aligned FF nanostructure was grown in FF concentrated water solution. In the process of forming the seed film, the polarization direction was aligned by applying an external electric field (Figure 5b). As a result, a vertically grown FF nanostructure having an aligned polarization direction was formed. In addition, the polarization direction could be controlled by controlling the direction of the external electric field during the self-assembly process, and the enhanced piezoelectric coefficient $d_{33}$ of 17.9 pm V$^{-1}$ was obtained.

Furthermore, polarized FF tubes based power generator produced the open-circuit voltage ($V_{oc}$), short-circuit current ($I_{sc}$), and power density of 1.4 V, 39.2 nA, and 3.3 nW cm$^{-2}$, respectively, under the application of 60 N of pushing force (Figure 5c,d).

In 2018, Lee et al. introduced a meniscus-driven self-assembly process to synthesize horizontally aligned and unidirectionally polarized FF nanostructures in a large area.\(^1\) Briefly, the substrate was dipped in FF solution, and self-assembled FF nanostructure was fabricated by pulling the substrate vertically from the solution (Figure 6a). The shape and morphology of the FF nanostructure was controlled by controlling the type of solvent, concentration of peptide solution, and

![Meniscus driven FF alignment](figure6.png)

**Figure 6.** Meniscus-driven horizontally polarized FF peptide nanotubes piezoelectric properties. a) Schematic of the fabrication process to create polarization controlled peptide nanotube arrays through meniscus driven self-assembly. b) Piezoelectric polarity controlled FF nanotubes on substrates. c) Generated piezoelectric peak voltages with 1 GΩ of load resistance and short-circuit currents of the FF nanotubes based piezoelectric energy harvesters as a function of applied force. Reproduced with permission.\(^1\) Copyright 2018, American Chemical Society.
pulling speeds of the substrates. The polarization direction of FF nanostructure was also controlled by control of the charge-dipole interaction between FF molecule and the substrate (Figure 6b). In addition, horizontally aligned FF nanostructure based energy generators were fabricated, and generated output $V_{oc}$, $I_{sc}$, and power of 2.8 V, 37.4 nA, and 8.2 nW, respectively. In addition, they demonstrated how to use the strong shear piezoelectric effect on the asymmetry shape of FF nanostructure in order to efficiently convert mechanical energy into electrical energy (Figure 6c).

The piezoelectric effect in a number of $\alpha$-helical polypeptides has also been reported.[101–106] Their piezoelectricity is mainly caused by the directional alignment of hydrogen bonds along the helical axis.[107] Fukada et al. in the 1970s reported the piezoelectricity in poly-$\gamma$-methyl-$\lambda$-glutamate (PMLG) and poly-$\gamma$-benzyl-$\lambda$-glutamate (PBLG) synthetic polypeptides.[108–111] In addition, theoretical and experimental studies on the piezoelectricity of $\alpha$-helix as well as $\omega$-helix and $\beta$-form synthetic polypeptides have been reported.[107,112] As with other piezoelectric materials such as amino acids, or FF, unidirectional polarization alignment is a very important issue for practical piezoelectric device applications. Therefore, several efforts have been made to fabricate polarized polypeptides through the application of an external magnetic field or electric field.[113–117] In 2004, the strong piezoelectric coefficient $d_{14}$ of 26 pC N$^{-1}$ was found in the PBLG membrane which was oriented by the application of a strong magnetic field (Figure 7a).[114] The piezoelectric coefficient was linearly increased with applied magnetic field, and it was not saturated at the magnetic field of 10 T. In addition, the fabrication of uniform and unidirectionally polarized PBLG-PMMA composite film by the application of external electric field through corona discharging and contact charging methods has been reported (Figure 7b).[115,118] The fabricated piezoelectric film exhibited strong piezoelectricity ($d_{33} = 23$ pC N$^{-1}$). In 2011, Farrar et al. fabricated permanently polarized PBLG fibers using electrospinning methods (Figure 7c).[119] The

![Figure 7a](https://www.advancedsciencenews.com/file/read_file/20/1906989/fig7a.png)  
Figure 7a. Schematic of the motion of PBLG molecules under the magnetic field. Reproduced with permission.[114] Copyright 2004, IOP Science.

![Figure 7b](https://www.advancedsciencenews.com/file/read_file/20/1906989/fig7b.png)  
Figure 7b. Schematics of the PBLG-PMMA composite film fabrication process and the structure of $\alpha$-helical polypeptide. Reproduced with permission.[113] Copyright 2008, Elsevier.

![Figure 7c](https://www.advancedsciencenews.com/file/read_file/20/1906989/fig7c.png)  
Figure 7c. Schematics of electrospinning and the PBLG poling process. The $\alpha$-helical molecular structure of PBLG is shown without side chains for simplicity. Small black arrows in the PBLG helix are individual hydrogen bonds, while long arrows under the PBLG helix and in the expanded portion of needle tip area represent the macroscopic dipoles of PBLG molecules. Reproduced with permission.[119] Copyright 2011, Wiley-VCH.
electrospun PBLG fiber showed a strong piezoelectric coefficient $d_{33}$ of 25 pC N$^{-1}$, and it was stable, even after 100 °C thermal treatment for over 24 h. These discoveries are great developments in the field of bio-piezoelectric materials, because a stable and strong $d_{33}$ piezoelectric constant is more favorable to the piezoelectric applications than shear mode piezoelectricity, such as $d_{14}$, $d_{15}$, and $d_{16}$, which is generally shown in bio-piezoelectric materials.

4. Piezoelectricity of Proteins

Proteins are complex macromolecules made up of amino acids with peptide bonds and exhibit piezoelectricity. Hundreds of combinations of 20 distinct amino acids linked by peptide bonds are possible, so many different kinds of proteins can exist. Each protein has a special function depending on its structure. In particular, numerous studies of piezoelectric proteins, such as collagen, keratin, prestin, and lysozyme, have been reported.

Collagen is the most abundant structural protein in mammals, accounting for 25–35% of the total protein components.[120] It is the main component of extracellular matrices and connective tissue including bone, tendon, cornea, and skin as well as joints, membranes of organs. Collagen structure is formed of three twisted polypeptides, and called a triple helix. Each polypeptide chain possesses a characteristic major tripeptide repeat (GPX) sequence with glycine (G), proline (P), and several different amino acids (X) (Figure 8a).[120–125] It was found that the piezoelectricity of collagen is due to this particular helical structure.[13,126–129] The static polarization in the longitudinal direction of collagen is due to helically aligned peptide bonding and the hydroxyl group present at the side chain of hydroxyprolines. The intensity of the polarization in the longitudinal direction changes due to the winding/unwinding motion of the structure when the physical force of compression/tension is applied, which is a piezoelectric effect.[129] In 2016, Zhu et al. reported the piezoelectric effect on the “super-twisted” collagen structure using atomistic simulation of super-twisted collagen, and verified the piezoelectric mechanism.[130] The result shows that collagen represents unidirectional polarization along the longitudinal axis of collagen fibril, and the magnitude of polarization is varied when mechanical stress is applied on the collagen due to the reorientation and magnitude change of the permanent dipoles. The calculated piezoelectric constant of collagen fibril ranged 1–2 pm V$^{-1}$. In addition, Sarah et al. in 2018 calculated the piezoelectric tensors of the building blocks of collagen: hydroxyl-l-proline, l-proline, and l-alanine, which are the most abundant l-amino acids found in collagen, using DFT-based quantum mechanical simulation (Figure 8b–d).[131] The predicted range of the piezoelectric strain constant was from <1 pC N$^{-1}$ (l-proline) to 28 pC N$^{-1}$ (hydroxyl-l-proline). The results show that increasing the molecule size and reducing the symmetry of the crystal control the piezoelectric tensors in a predictable manner. Therefore, these results could be considered in the design of the dimer and

Figure 8. Piezoelectricity of collagen. Structure and piezoelectricity of a) collagen amino acids, b) collagen peptide, c) collagen triple helix, and macroscopic collagen. Reproduced with permission.[131] Copyright 2018, Royal Society of Chemistry. e) Schematic shows the fabricated collagen fibrils based piezoelectric device. f) Output voltage and current response of collagen fibrils based piezoelectric energy generators. Reproduced with permission.[143] Copyright 2018, American Chemical Society.
trimer bio-piezoelectric crystals for future piezoelectric applications. The quantitative analysis of piezoelectricity on collagen fibrils has also been performed using resonance measurement and the PFM method.[132–139] In 1999, Goes et al. reported the collagen films extracted from bovine serosa exhibit piezoelectric charge coefficient $d_{14}$ of 0.096 pC N$^{-1}$, measured by the resonance measurement method.[140] Afterward, Yu et al. reported the piezoresponse of the individual type I collagen fibrils with diameters of $\approx$100 nm isolated from bovine Achilles tendon using the lateral mode PFM method.[141] Collagen fibers were found to have unipolar axial polarization and mainly acted as shear piezoelectric materials, with piezoelectric constants $d_{15}$ of $\approx$1 pm V$^{-1}$. Furthermore, the piezoresponses at the length scale of an individual collagen fibril from rat tail tendons were obtained by the measuring of angle-dependent in-plane and out-of-plane piezoresponse using PFM.[126] The piezoelectric tensors $d_{ij} = 0.89$ pm V$^{-1}$, $d_{31} = -4.84$ pm V$^{-1}$, $d_{14} = -12$ pm V$^{-1}$, and $d_{45} = 6.21$ pm V$^{-1}$ were obtained, which values are in good agreement with the values obtained by simulations. It was also found that the piezoelectricity of collagen is also affected by pH and humidity, because they change the activity of the polar bonds of collagen and crystal structure.[142] These studies show that the piezoelectric properties of collagen vary greatly depending on how the collagen is isolated from the tissue, and how it is prepared. The reason for this is that the piezoelectric properties of the collagen film vary greatly depending on the polar bond of the building blocks, type of amino acids, crystallinity, and alignment of the macro-micro structured collagen. In 2018, Vivekananthan et al. demonstrated for the first time collagen film based piezoelectric energy generators (Figure 8e,f).[143] The piezoelectric energy generator was fabricated by attaching two conducting films on the top and bottom side of the collagen film and laminating using a polypropylene. The resulting output performance of the collagen-based piezoelectric generator varies with the thickness and density of the collagen because the improper distribution of collagen fiber reduces the electrical output. It produced maximum $V_{oc}$ and $I_{sc}$ of 50 V and 250 nA, respectively, upon the application of 5 N force, and can also work as a self-powered relative humidity sensor with good sensitivity (0.1287 µA % RH$^{-1}$) in the range of 50–90%. These results demonstrate the potential of biocompatible collagen as a multifunctional material for future biomedical applications.

The piezoelectric characteristics of other piezoelectric proteins, such as keratin, prestin, and lysozyme have also been studied. Keratin is a right-handed $\alpha$-helical fibril structured protein, typically high in alanine, leucine, arginine, and cysteine, which is found in skin, hair, and nails.[144,145] In 1940, the piezoelectricity of keratin was first reported by detecting the electric charges produced on the surface of wool and human hair when mechanical stress is applied.[10] This is also claimed to be due to the synergistic alignment of its $\alpha$-helical dipoles of CONH in the axial direction of the ordered structure in keratin (Figure 9a),[146,147] and was proved by investigating the piezoelectric property and crystal structure of keratin depending on temperature.[148] Fukada et al. showed that the piezoelectric property of keratin rapidly decreases at temperature above 200 °C. Fourier transform infrared (FTIR) measurements showed the $\alpha$-helical dipoles were in antiparallel conformation without polarity. Prestin, the motor protein of the outer hair

![Figure 9](image-url)
cells (OHCs) of the mammalian cochlea, also exhibits strong piezoresponse even though it does not have helical structure.[11,149–156] OHCs have high-frequency cell motility driven by potential changes that amplify sound-induced vibrations, which are produced by prestin, a membrane protein that acts as an electromechanical transducer. The piezoelectric property of OHC was experimentally demonstrated by observing OHC contraction and elongation in response to depolarization and hyperpolarization controlled by stimulation (Figure 9b). In addition, the piezoelectric coefficient of the prestin was also examined by measuring the charge displacement induced by force, and the coefficient reached ≈20 mC N⁻¹ for 50 µm long lateral membrane, which is much greater value than that of the conventional piezoelectric materials (Figure 9c).[157] The piezoelectric mechanism of the prestin and OHC is not yet fully understood, and different from that of conventional piezoelectric materials. However, the exceptionally large piezoelectric coefficient of the cell demonstrates the unique role of the cell as a piezoelectric motor of biological importance, and it also indicates its potential applications for highly efficient biocompatible energy generators. Lysozyme, the antibacterial enzyme found in mammalian tears, saliva, and milk, also exhibits piezoelectric response.[158,159] In 2017, Stapleton et al. reported lysozyme can form two different crystalline structures, monoclinic and tetragonal, with piezoelectric properties, and the measured average piezoelectric coefficients were 0.94, and 3.16 pC N⁻¹, respectively (Figure 9d).[160] The maximum piezoelectric coefficient of 6.5 pC N⁻¹ was reached for the tetragonal aggregate film of lysozyme. In 2018, they also measured piezoelectric response using the PFM method from the tetragonal structure lysozyme, which response reached 19.3 pm V⁻¹.[161] In addition, it is also found that the noncrystalline form of lysozyme shows a switchable polarization that is ferroelectric behavior. These findings have raised interest in the biophysiological significance of piezoelectricity on lysozyme, and its future potential applications.

5. Piezoelectricity in the Human Body

Many components of the human body exhibit piezoelectric properties including bone, tendon, ligament, cartilage, skin, dentin, cornea, and sclera. Their significance of piezoelectric functions in living cells has also been reported.[5,8,9,17,21,23,24,148,162–164] One of the reason why living cells exhibit piezoelectric properties is that their structures consist of piezoelectric proteins.[12,126,129,144,165] In 1957, Fukada investigated the quantitative piezoelectric property of bone by means of both direct and converse piezoelectric effects, and found that the value of the piezoelectric constant is about one-tenth that of quartz.[5] In addition, it was found that the piezoelectric property of bone disappeared after decollagenation, but still had piezoelectricity after demineralization.[165] It was proved that the origin of piezoelectricity in bone comes from the piezoelectric collagen. The electricity generated through piezoelectric effect of collagen is known to be essential for bone regeneration. However, bone-repair function has also been observed near cracks at the surface of pure hydroxyapatite ceramics where there is no piezoelectricity. It was hypothesized that hydroxyapatite ceramics could also generate electricity due to flexoelectricity, which is a charge generation by strain gradient, even though there is no piezoelectric effect.[25] Therefore, we believe that the study of the flexoelectricity in the human body for the effect of tissue regeneration is also considered a very intriguing and significant topic in the future.

The tendon also exhibits piezoelectricity. The piezoelectric effects in the Achilles tendons of cow and horse were shown to be much stronger than that of bone, due to the collagen

![Figure 10](https://www.advancedsciencenews.com/1906989)
being aligned in a good orientation along the long axis of the tendon.\cite{126} Investigation of the piezoelectric properties of rat tail tendons depending on the angle in nanoscale using PFM method proved that the origin of piezoelectricity in the tendon was also due to the oriented collagen fibrils (Figure 10). The cornea and sclera were also known to exhibit piezoelectricity because they consist of collagen.\cite{12,13,166} The corneal tissue has an orthogonally aligned collagen layer structure, while the sclera has randomly orientated layered structures. The piezoelectric response of corneas observed anisotropically, and the piezoelectric coefficient of the diagonally, vertically, and horizontally cut samples were observed with average values of 2250, 600, and 200 pC N\(^{-1}\), respectively (Figure 11).\cite{12} Due to the random orientation of the collagen structure, the sclera exhibit a significantly lower piezoelectric constant (31.8 pC N\(^{-1}\)). The interesting point about piezoelectricity in the cornea and sclera is that as they dehydrate, the piezoelectricity is significantly reduced. It is known that piezoelectric constant of collagen vary significantly with hydration.\cite{135,167} The skin is also a well-known piezoelectric living tissue in the human body. In 1967, piezoelectricity on the skins from human, cat, and pig was measured by Shamos et al. and was speculated to be due to the oriented collagen fibrils. In 1982, the pyroelectric and piezoelectric properties of the epidermis of human skin prepared from intact skin consisting of epidermis and corium were discovered (Figure 10e).\cite{162} It was found that the outer and inner skin surface responded with opposite sign to each other by the application of mechanical stress and rapid temperature changes; the skin is thus polar. In this work, polar behavior was represented in the epidermis, but no polar property was found for the corium. It was assumed that the polar behavior of the epidermis is caused by polar keratin filaments that are oriented perpendicular to the dermal–epidermal junction in the cell layers. In addition, the authors compared the piezoelectric properties between fresh skin and dry skin. The signal from dry skin was 20–60% smaller than that from fresh skin, but showed that the piezoelectric property was mainly due to a physical material property, but was not dependent on the living state. In 1986, Rossi et al. performed quantitative study of the piezoelectric properties on skin. This work investigated the piezoelectricity in each layer of skin, dermis, epidermis, and horny layer, and found the origin of the piezoelectric properties of each layer.\cite{9} The schematic of skin structure with horny layer, dermis, and epidermis is shown in Figure 10f. The author found that piezoelectricity on the dermis originated from the piezoelectricity of collagen, and the epidermis and horny layer are caused by piezoelectric keratin. The maximum piezoelectric constants of each dermis, epidermis, and horny layer were measured to be 0.1 C N\(^{-1}\), 0.03 pC N\(^{-1}\), and 0.2 pC N\(^{-1}\), respectively.

6. Summary and Perspective
In this review, we have summarized the progress in various biological piezoelectric materials including amino acids, peptides, proteins, and living tissues. We believe that this review will provide useful insight to design piezoelectric materials and applications of biological piezoelectric materials. In order for the material to exhibit piezoelectric properties, that material must have a specific form (non-centrosymmetric, asymmetrical structure) that has no center of symmetry in the crystal structure of the material. Interestingly, various parts of the human body, such as bone, tendon, cartilage, ligament, hair, skin, and cochlea, exhibit piezoelectric properties. The reason why various living tissues of the human body exhibit piezoelectric properties is because living tissues consist of biomolecules with piezoelectricity. If the living tissues form appropriate structures, they can exhibit piezoelectricity. Various piezoelectric biomolecules, such as amino acids, peptides, and proteins, are abundant and inexpensive materials. These biomolecules are biocompatible piezoelectric materials that can have great advantages in future biomedical applications.
has been reported that certain biological piezoelectric materials exhibit strong piezoelectricity that is comparable to that of conventional piezoelectric materials (Table 1). Another main advantage of using biological piezoelectric materials for piezoelectric applications is their relatively low dielectric constant compared to the conventional piezoelectric materials because the piezoelectric voltage constant ($g_{ij}$) is inversely proportional to the dielectric constant according to the following equation:\(^{[168-170]}\)

$$g_{ij} = \frac{d_{ij}}{\varepsilon} \tag{1}$$

where $d$ is the piezoelectric strain constant, $g$ is the piezoelectric voltage constant, and $\varepsilon$ is the dielectric constant. Although the discovered bio-piezoelectric materials exhibit strong piezoelectric property, research on the piezoelectric properties of biomolecules still require further studies that accurately analyze the piezoelectric mechanism. Currently, most challenging issues for the development of strong bio-piezoelectric materials and realization of its applications such as sensors, actuators, and energy harvesters are their limited patterning, control over the orientation, and polarization directions. Recently, in order to solve these problems, bio-piezoelectric materials based self-assembly, inkjet printing, 3D printing, and electric field induced alignment method have been attempted.\(^{[85,99,100,171-177]}\)

In addition, unlike robust conventional inorganic piezoelectric materials, the development of instrument to analyze soft bio-piezoelectric materials is also very significant for the fundamental studies and applications of bio-piezoelectric materials.\(^{[178,179]}\)

The piezoelectric biomolecules present in the human body are known to have a close relationship with human health in various parts. For example, the piezoelectric properties of collagen have been shown to affect the growth, healing, and remodeling of bones. In addition, there are a lot of living tissues cells such as tendon, cartilage, ligament, hair, skin, and cochlea, which are composed of various piezoelectric biomolecules, and the piezoelectricity on these living tissues is expected to be closely related to the human health condition. Furthermore, from the above biomolecules and tissues, a number of studies have previously shown biological ferroelectric properties. Bio-ferroelectricity is control of the polarization direction by an externally applied electric field in biomolecules.\(^{[180,181]}\) It is well known that piezoelectricity is closely related to ferroelectricity. However, the biological significance of bio-ferroelectricity is not poorly understood.

## Table 1. Piezoelectric materials based on biomolecules.

<table>
<thead>
<tr>
<th>Bio/piezoelectric materials</th>
<th>Type</th>
<th>Piezoelectric coefficient</th>
<th>Features</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycine</td>
<td>Amino acid</td>
<td>$d_{11} = 178 \text{ pC N}^{-1}$</td>
<td>Calculated</td>
<td>[71]</td>
</tr>
<tr>
<td>Alanine</td>
<td>Amino acid</td>
<td>$d_{33} = 17.75 \text{ pC N}^{-1}$</td>
<td>$\alpha$-alanine, Calculated</td>
<td>[63]</td>
</tr>
<tr>
<td>Proline</td>
<td>Amino acid</td>
<td>$d_{33} = 27.75 \text{ pC N}^{-1}$</td>
<td>Hydroxy-$\alpha$-proline, $\alpha$-amino acid found in collagen Calculated</td>
<td>[131]</td>
</tr>
<tr>
<td>Threonine</td>
<td>Amino acid</td>
<td>$d_{33} = 4.9 \text{ pC N}^{-1}$</td>
<td>Longitudinal piezoelectric response ($d_{33} = 0.1 \text{ pC N}^{-1}$)</td>
<td>[62]</td>
</tr>
<tr>
<td>Asparagine</td>
<td>Amino acid</td>
<td>$d_{11} = 13 \text{ pC N}^{-1}$</td>
<td>$\alpha$-Asparagine Calculated</td>
<td>[71]</td>
</tr>
<tr>
<td>Leucine</td>
<td>Amino acid</td>
<td>$d_{11} = 12.5 \text{ pC N}^{-1}$</td>
<td>$\alpha$-Leucine Calculated</td>
<td>[71]</td>
</tr>
<tr>
<td>Histidine</td>
<td>Amino acid</td>
<td>$d_{11} = 18 \text{ pC N}^{-1}$</td>
<td>$\alpha$-Histidine Calculated</td>
<td>[71]</td>
</tr>
<tr>
<td>Methionine</td>
<td>Amino acid</td>
<td>$d_{11} = 15 \text{ pC N}^{-1}$</td>
<td>$\alpha$-Methionine Calculated</td>
<td>[71]</td>
</tr>
<tr>
<td>Aspartate</td>
<td>Amino acid</td>
<td>$d_{11} = 13 \text{ pC N}^{-1}$</td>
<td>$\alpha$-Aspartate Calculated</td>
<td>[71]</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>Amino acid</td>
<td>$d_{11} = 25 \text{ pC N}^{-1}$</td>
<td>$\alpha$-Isoleucine Calculated</td>
<td>[71]</td>
</tr>
<tr>
<td>Cysteine</td>
<td>Amino acid</td>
<td>$d_{22} = 11.4 \text{ pC N}^{-1}$</td>
<td>$\alpha$-Cysteine Calculated</td>
<td>[71]</td>
</tr>
<tr>
<td>FF</td>
<td>Peptide</td>
<td>$d_{11} = 80 \text{ pC N}^{-1}$</td>
<td>Size dependent</td>
<td>PFM method</td>
</tr>
<tr>
<td>PBLG</td>
<td>Peptide</td>
<td>$d_{11} = 25 \text{ pC N}^{-1}$</td>
<td>Longitudinal piezoresponse Electrosprin PBLG</td>
<td>Quasi-static method</td>
</tr>
<tr>
<td>PMLG</td>
<td>Peptide</td>
<td>$d_{14} = 2 \text{ pC N}^{-1}$</td>
<td>Quasi-static method</td>
<td>[24]</td>
</tr>
<tr>
<td>PLLA</td>
<td>Peptide</td>
<td>$d_{14} = 10 \text{ pC N}^{-1}$</td>
<td>Quasi-static method</td>
<td>[24]</td>
</tr>
<tr>
<td>Collagen</td>
<td>Protein</td>
<td>$d_{14} = 12 \text{ pC N}^{-1}$</td>
<td>Collagen from rat tail tendon</td>
<td>PFM method</td>
</tr>
<tr>
<td>Keratin</td>
<td>Protein</td>
<td>$d_{14} = 1.8 \text{ pC N}^{-1}$</td>
<td>Quasi-static method</td>
<td>[24]</td>
</tr>
<tr>
<td>Prestin</td>
<td>Protein</td>
<td>$d_{13} = 20 \text{ mC N}^{-1}$</td>
<td>Membrane in the outer hair cell</td>
<td>Quasi-static method</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Protein</td>
<td>$d_{13} = 6.5 \text{ pC N}^{-1}$</td>
<td>Longitudinal piezoresponse</td>
<td>Quasi-static method</td>
</tr>
<tr>
<td>Bone</td>
<td>Tissue</td>
<td>$d_{13} = 0.2 \text{ pC N}^{-1}$</td>
<td>Quasi-static method Collagen base</td>
<td>[5]</td>
</tr>
<tr>
<td>Tendon</td>
<td>Tissue</td>
<td>$d_{14} = 2 \text{ pC N}^{-1}$</td>
<td>Quasi-static method Collagen base</td>
<td>[20]</td>
</tr>
<tr>
<td>Epidermis</td>
<td>Tissue</td>
<td>$d_{14} = 0.03 \text{ pC N}^{-1}$</td>
<td>Quasi-static method Keratin base</td>
<td>[9]</td>
</tr>
<tr>
<td>Dermis</td>
<td>Tissue</td>
<td>$d_{14} = 0.1 \text{ pC N}^{-1}$</td>
<td>Quasi-static method Collagen base</td>
<td>[9]</td>
</tr>
<tr>
<td>Cornea</td>
<td>Tissue</td>
<td>$d_{13} = 2250 \text{ pC N}^{-1}$</td>
<td>Quasi-static method Decreased with dehydration</td>
<td>[12]</td>
</tr>
</tbody>
</table>
D.K. and S.A.H. contributed equally to this work. This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2018R1C1B5086524 and No. 2019R1F1A1060733), and the DGIST Start-up Fund Program of the Ministry of Science, ICT and Future Planning (No. 2019010076).

Conflict of Interest
The authors declare no conflict of interest.

Keywords
amino acids, peptides, piezoelectricity, proteins, tissues

Received: October 24, 2019
Revised: December 16, 2019
Published online:
