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Review

Natural vs Synthetic Polymers: How Do They Communicate with Cells for Skin Regeneration—A Review

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Abstract: Modern research has evolved several approaches toward skin regeneration and one of the novel concerns is the use of polymer-based systems due to their excellent beneficial properties to the skin. Several polymers, such as cellulose, hyaluronan, alginate, chitosan, collagen, fibrin and fibroin, have been tested and have proven the benefits for skin regeneration, and most of them are derived from either polysaccharide- or protein-based materials. In order to understand the mode of action, several researchers investigated the cell–matrix interaction and possible signaling mechanism in skin regeneration. Not only the signaling mechanism but also the mode of cell communication determines the application of polysaccharide- and protein-based polymers in practice. Based on the above significance, this review disclosed the recent findings to compile a possible method of communication between cells and polymers derived from polysaccharide-based (such as cellulose, hyaluronan, chitosan, alginate, agar, and xanthan gum) and protein-based (such as collagen, gelatin, fibrin, and silk fibroin) materials along with other polymers, such as poly(vinyl alcohol), polyglycolide or poly(glycolic acid), or poly(lactic acid) in skin regeneration. Accordingly, this review addresses the fundamental concept of cell–matrix communication, which helps us to understand the basis of the polymer's functions in the biomedical field.

Keywords: natural polymers; synthetic polymers; skin regeneration; fibroblasts; cell–matrix communication

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1. Introduction

The use of polymers in the tissue engineering field has dramatically increased in recent years due to their successful outcomes. More studies are emerging to finalize proper polymers without any adverse effects. In fact, both synthetic and natural polymers have been tried to confirm the safety of different polymers. In most cases, the polymers are fabricated as composites in order to improve the physiological state and biological functions. Recent research is focusing on investigating the actual mode of action of polymers in biological processes and exploring how the polymers interact with biological cells in order to facilitate regenerative action.

The anchoring behavior of polymers determines the mode of interaction and certain cellular signaling pathways for cellular activities, such as cellular proliferation, differentiation, and migration [1,2]. The actual binding mechanism of polymers with cell receptors can be determined using a high-throughput (HT) microfluidic platform along with microarray-based biosensor methods [3]. The cell–matrix interaction is enabled by the mechanical and porous structural network of the polymers to achieve successful tissue regeneration

and restoration. The assessment of cell–polymer interaction depends on the molecular components and molecular weight of polymers [4]. The cell–polymer interaction facilitates ECM remodeling after the transplantation [5].

In this sense, several materials, such as naturally derived materials collagen, gelatin, chitosan, hyaluronan, fibrin, chondroitin sulfate, and fibroin as well as the synthetically derived materials PVA, PLA, PGA, and PLLA—have been tested in biomedical applications, especially in skin regeneration [6,7].

In most cases, the polymers are used as a novel carrier for delivering specific drugs to target tissue, and this targeted delivery system aims to increase the efficacy of drugs without reducing off-target effects. In this case, polymers serve as ideal delivery vehicles for multiple therapies due to their intrinsic properties and functional moieties [8]. For instance, nanoparticles loaded with chondroitin sulfate were specifically targeting CD44 expressed macrophages to reduce the inflammation in ulcerative colitis both in vitro and in vivo compared to non-coated counterparts [9]. The positively charged chitosan facilitates electrostatic interactions with negatively charged cell surfaces [10].

Based on the raw materials, the mode of interaction of polymers differs in biological pathways. For instance, the naturally derived materials interact with cell membranes through different receptors, such as integrins, DDR, OSCAR, and other plasma-protein-based membrane receptors [11]. However, synthetic-based polymers facilitate membrane attachment through electrostatic, hydrophobic, and hydrogel bonds. From the above hypothesis, it is clear that the receptor interaction pattern and communication of biological cells may differ between natural and synthetic polymers. Therefore, it is very important to understand the cell–matrix interaction in order to advance the biomaterial's use in practical applications. The recognition pattern of polymers in cell receptors determines the intrinsic properties of materials and thereby their drug delivery modes. Hence, the drug delivery mechanisms of materials can be manipulated by adjusting the materials' properties and active receptor motifs [12]. Based on the above concepts, it is very important to understand the mechanism of cellular receptor's interaction with materials used for therapeutic application, especially for skin regeneration. Therefore, this review is specifically focused on compiling the possible methods of cellular receptor interaction with natural and synthetic materials used in skin regeneration.

2. Natural Polymers Used in Skin Regeneration

2.1. Protein-Based

2.1.1. Collagen

Collagen is one of the most used polymers in the tissue engineering field, and its unique properties make them more attractive in skin regeneration [13]. Collagen is used in skin regeneration in different forms such as films, gels, scaffolds, mats, composites, and 3D matrices. Several studies proved the exceptional characteristics of collagen in skin regeneration regardless of the above-mentioned forms [14,15]. The unique features of collagen, such as mechanical strength, degradation, water absorption, and biocompatibility, have attracted many researchers for several decades. The controlled degradation of collagen-based material is an exceptional property to be used in skin regeneration [16]. Conventional collagen was previously isolated from only land-based animals and after contagious disease outbreaks, alternative sources, such as marine-based animals, are currently used for collagen extraction [17]. However, the stability and physicochemical properties are not sufficient compared to mammalian collagen, and several crosslinking strategies are proposed to compensate for the standard requirements in practical applications.

Advantages and Limitations

The major advantages of collagen in skin regeneration are self-regeneration, biocompatibility, biomimetics, proliferation, mineralization, degradation, flexibility, moisturization, and skin repair. The limitations of collagen used in skin applications are inadequate mechanical properties (compared to other polymers), susceptibility to degradation by

local enzymes in the skin, low levels of adverse and cytotoxic effects, and sometimes insufficient action.

2.1.2. Gelatin

Gelatin is a denatured form of collagen and has a similar impact in the tissue engineering field as collagen. Due to its suitable biodegradability and biocompatibility in physiological environments, gelatin is a common natural polymer used in medical and pharmaceutical applications [18–20]. In contrast to collagen, gelatin has relatively low antigenicity due to its denatured form [21]. Similar to collagen, the characteristics of gelatin, such as degradation rate, mechanical properties, and drug-releasing behavior, were modified by the crosslinking density of gelatin [22]. Due to its controlled drug delivery, gelatin has been widely studied for skin tissue engineering [23]. For instance, the beneficial effect of gelatin on skin regeneration was previously investigated by several researchers [24,25].

Advantages and Limitations

The major advantages of gelatin in skin applications are skin cell growth, migration, adherence and regeneration, maintaining skin integrity, growth factor stimulation, endothelial cell induction, and hemostatic and unfavorable effects on cellular and mechanical properties [25–27].

2.1.3. Fibrin

Fibrin is a complex network formed by the polymerization of fibrinogen, which is present in blood plasma in the presence of the enzyme thrombin. Due to its unique structure and composition, fibrin has been used in general for limiting immunogenic reactions and the potential for disease transmission [21]. Fibrin is occasionally present in a temporary matrix during the regeneration involved in the extracellular matrix. Fibrin is used in clinical applications in the form of glue as a carrier for growth factors for enhancing healing and subsequently accelerating repair processes [28,29]. Fibrin is often fabricated as a hydrogel in order to facilitate moisture content, biocompatibility, mechanical properties and controlled drug delivery for various cells, including keratinocytes, fibroblasts [30], and mesenchymal stem cells [31].

Advantages and Limitations

The major advantages of fibrin in skin regeneration are biocompatibility, maintaining moisture content, improving cell growth, controlled drug delivery, and regenerative ability. The major limitations are rapid degradation in vivo, poor structural integrity, instability and solubility over time, and undesired crosslinking with other artificial scaffolding material [31–33].

2.1.4. Silk Fibroin

Silk fibroin (fibrous protein) is a natural protein present in insects, such as silkworms, spiders, and sea animals [34,35]. Naturally, it is encapsulated with sericin (a glue-like protein) as a protective layer, and pure fibroin is extracted by removing sericin after performing degumming procedures on raw silk fibers. Silk fibers are made up of 17 amino acids of fibroin together with sericin. Silk fibroin has excellent regenerative properties and mechanical properties without adverse effects, which allow them to be used in many biomedical applications in different forms such as fiber mats, hydrogels, scaffolds, and 3D matrices. Due to its high tensile strength, fibroin materials are widely used in skin closure sutures [36].

Advantages and Limitations

The benefits of fibroin in the skin are regeneration, self-healing, biocompatibility, mineralization, re-epithelialization, biosynthesis of collagen, enhanced elimination of scarring, anti-inflammatory activity, minimal immunogenicity, and maintenance of homeostasis [37].

The limitations are poor electrospinning, cross-contamination with sericin, and excessive precautions in extraction [21].

2.2. Polysaccharide-Based

2.2.1. Hyaluronan

Hyaluronan is a constituent of the ECM and pericellular matrices comprising non-sulfated glycosaminoglycan, which plays a major role in embryo development, cell proliferation and other cellular dynamic events. It is composed of alternating (1-4)-β-linked D-glucuronic and (1-3)-β-linked N- acetyl-D-glucosamine residues [38]. It interacts with other extracellular macromolecules and proteoglycans to facilitate cell migration, proliferation, ECM assembly, and pericellular matrix assembly, activating and moderating the inflammatory response and reducing scar formation and wound healing [12,39,40].

The molecular weight of hyaluronan influences its biological function—for instance, hyaluronan with high MW promotes anti-angiogenic, anti-tumorigenesis, and anti-inflammatory responses in breast cancer cell lines, whereas lower-MW hyaluronan is implicated in CD44 cleavage, angiogenesis, and cell motility. The hyaluronan improved the survival and integration of retinal stem cell-derived rods in the retina by interacting with CD44 receptors of retinal-stem-cell-derived rod cells [6,41].

Advantages and Limitations

The hygroscopic nature, mechanical stability, high molecular weight, cell surface receptor interaction, and reduced scar formation of HA provide an ideal feature for skin regeneration applications [42,43]. Due to its negative charge and excellent swelling capacity, hyaluronan delivers the controlled drug release of biomolecules [44]. The major limitations for producing scaffolds and tailored composite polymers lie in the control of their rheological properties and viscosity and are thus typically associated with other polymers with fewer gel characteristics [45].

2.2.2. Chitosan

Chitosan, the second-most abundant polysaccharide in nature (after cellulose), is one of the most studied polysaccharide polymers in tissue engineering due to its biocompatible nature, biodegradability, and low or nonexistent cytotoxicity/toxicity [46]. Is obtained through the deacetylation of chitin and is composed of N- acetyl glucosamine units linked by (one to four) glycosidic bonds [47]. It is mainly extracted from the exoskeletons of crustaceans such as shrimps and crabs and the cell walls of fungi [48]. Additionally, chitosan can be readily solubilized in weakly acidic media, facilitating handling under mild conditions, allowing electrostatic interaction and binding to proteins, polyanions, i.e., synthetic polymers or extracellular matrix components and DNA. Additionally, once solubilized, it can be transformed into tailored morphologies and shapes. Indeed, in the form of hydrogels, chitosan can be extruded, gelled, and crosslinked using neutralizing bases, such as sodium hydroxide (NaOH) [49–51]. The antibacterial effect of chitosan has been well established by several works [52]. Chitosan is widely combined with several polymers (synthetic and natural) and essential oils [53–56]. Additionally, due to its intrinsic physicochemical characteristics, it can be readily transformed into membranes, films, hydrogels, micro- or nanoparticles, and even into porous scaffolding systems [49–51,57,58].

Advantages and Limitations

Chitosan has been widely used for 3D printing but not for bioprinting because the processing conditions are not cell-friendly [59]. Chitosan exhibits very low mechanical strength, lower porous structure and very poor water solubility (needs an acidic environment). Additionally, typically, all these physicochemical properties are affected by crosslinking used during solubilization and material processing [43]. Different routes have been explored to overcome all the former disadvantages, including but not limited to

association with other polymers modules, structure and morphology, combination with plasticizer to enhance swelling rate, and water vapor permeability, among others.

2.2.3. Alginate

Alginate is a naturally occurring polysaccharide composed of a basic repeat unit consisting of linear anionic polysaccharide polymer of β-(1-4)-D-mannuronic (M-blocks) and α-l-guluronic acid (G-blocks) and is found in brown algae and some bacteria [60]. It is structurally organized in a blockwise pattern with alternating MG units [61]. It has been used as hydrogel [62], bilayer film [63], membranes [61], and wound dressings [64].

Advantages and Limitations

The main drawback of using alginates as a polymeric matrix relates to their lack of mechanical strength, poor cell adhesion, and stability, resulting in ion leaching [65]. As typical for natural polysaccharides, often must be associated or blended with other polymers, biopolymers or synthetic polymers with improved thermal, mechanical and solubility parameters in order to improve mechanical strength, stability, and biological response such as cell adhesiveness properties [43].

2.2.4. Cellulose

Cellulose is the most abundant polysaccharide-based naturally derived polymer on Earth and can be found in plants as well as several microbes [66]. However, as far as our knowledge is concerned, wood is the primary source for industrial purposes [67]. Cellulose has been widely used in healthcare products, specifically in skincare products because of its high functionality, biocompatibility, and biodegradability [67–69]. Cellulose's physicochemical, biochemical, and biological functions vary dramatically depending on the source. Despite its acceptable biocompatibility, cellulose typically does not have relevant antimicrobial properties without the addition of active antibacterial biomolecules [69]. However, it has been reported that this can be overcome by using extracted cellulose from different plants from Ecuador [69]. Cellulose has been widely used to produce polymers for tissue engineering applications and skin regeneration, including but not limited to hydrogels [69–72], films [73], nanofibrous wound dressing [74], non-woven composites [75], 3D-printed scaffolds [76], and fiber bats [77] among others.

Advantages and Limitations

Typical disadvantages related to this natural polymeric precursor are related to its lower mechanical flexibility, Young's modulus and weak mechanical strength. Additionally, cellulose exhibits poor antibacterial properties but also deficient water/oxygen vapor permeability. A very important issue due to sustainability concerns is about using hazardous solvents/reagents during its production. Indeed, currently, highly appealing novel green synthesis routes promote low energy consumption and also decrease production costs [67–69].

2.2.5. Agar

Agar is a natural biopolymer obtained from algae [78]. It has been proven to have excellent biocompatibility and biodegradability properties but also exhibits good mechanical properties, allowing it to form matrices with various beneficial effects. Additionally, it can be transformed into complex micro/macrostructures [79]. Their uses in biomedicine and skin regeneration include but are not limited to the development of scaffolds [80], hydrogel substrates [81,82], membranes [83], injectable composite hydrogels [84], or carriers for tissue engineering, mainly due to their great potential bioactivity, biocompatibility, and biodegradability [82]. Its porous 3D structure allows its use in biomolecular separation and purification [82]. Additionally, the three-dimensional networks of agar bear a similar structural resemblance to that of the extracellular matrix (ECM) of tissues. Additionally, one of their main advantages is that they do not release cytotoxic by-products during their

biodegradation. In addition, they are biocompatible/bioactive, which means these materials are capable of promoting cell adhesion and proliferation. Additionally, agar-based polymers have a high melting temperature (around 90 °C), allowing microorganisms to grow at higher temperatures than their counterpart and main competitor as a biocompatible matrix, which is gelatin. They are also transparent and resistant to digestion by enzymes produced by bacteria [78,82].

Advantages and Limitations

A disadvantage of agar is its severe electroendosmosis unless its sulfur content is removed before use. Additionally, as a support medium, its main drawback includes but is not limited to slow diffusion and bad contrast [78,82].

2.2.6. Xanthan Gum (XG)

Xanthan gum (XG) is used as a natural polymer in various commercial formulations in the pharmaceutical and biomedical industries [82] and is obtained from fermentation by microbial sources (bacterium Xanthomonas campestris) of sugar. XG consists of the chain β1-4-linked and repeating D-glucose units and a side-chain of D-mannose and D-glucuronic acid. Its uses include but are not limited to scaffolds, electrospun nanofiber-mats [85], hydrogels [86], aerogels [87], gels, microgel emulsions [88], 3D-printed substrates [89], 3D-printed carriers for tissue engineering, and in skin regeneration, mainly due to its great potential bioactivity, biocompatibility, and biodegradability. Among the advantages resulting from the use of such natural polysaccharides are polymeric precursors, low cost, almost nonexistent release of cytotoxic by-products, and the ability to support cell adhesion and proliferation. Additionally, XG is water-soluble at room temperature but is also soluble in glycerol at 65 °C [43].

Advantages and Limitations

XG is hydrosoluble at lower concentrations. Due to its nutrient-rich nature, it degrades readily and therefore often must be associated with preservatives to avoid the presence of undesired microorganisms. Variable rheological properties were strongly dependent on their physicochemical parameters, temperature, ionic strength, and pH. It also lacks thermal and mechanical stability, so it is frequently used in association with biopolymers or synthetic polymers with superior mechanical, thermal, and solubility properties. Finally, it can be chemically modified or crosslinked in order to meet the desired biological functionality for skin and tissue regeneration [43]. Figure 1 shows the most used natural (protein-based and polysaccharide-based)/synthetic polymers used in skin and tissue engineering regeneration and repair.

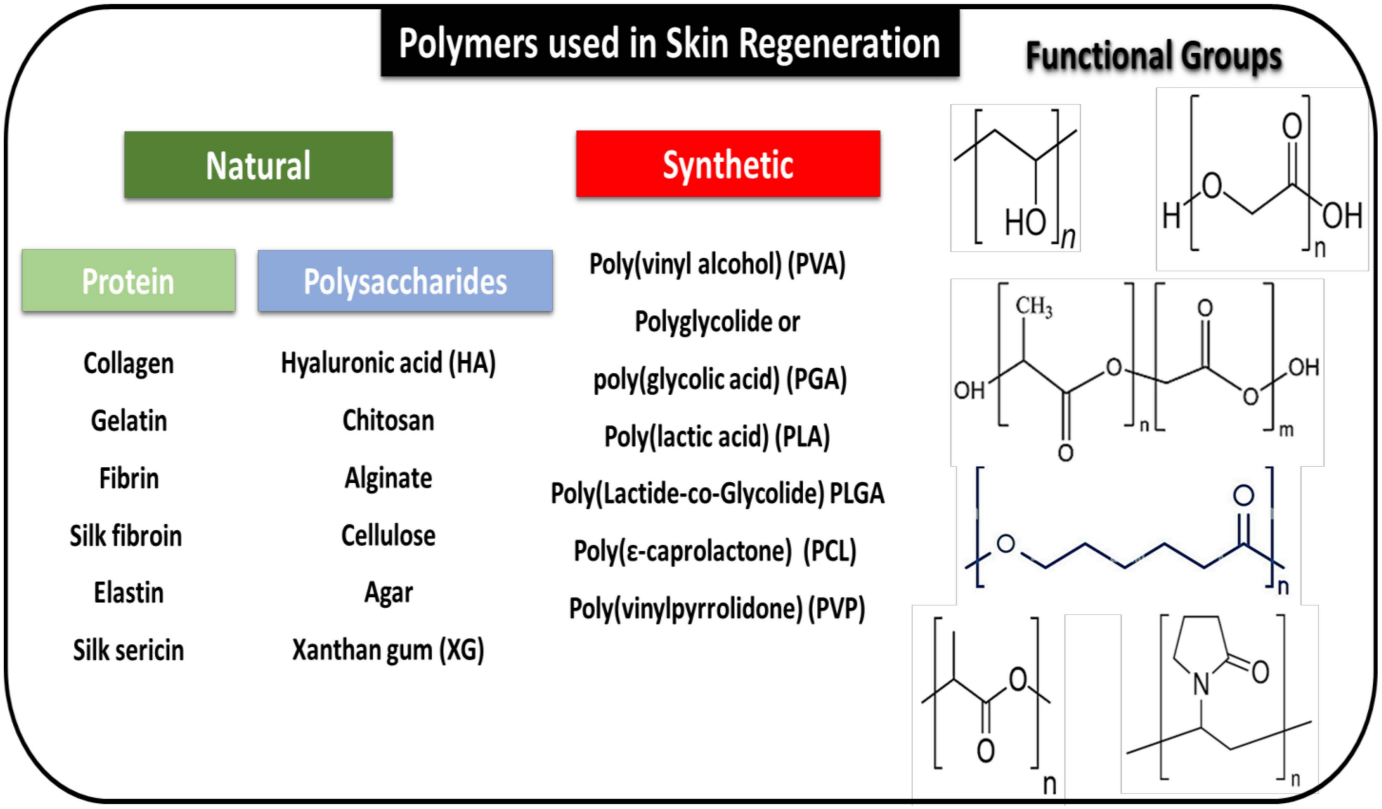

Figure 1. Typical natural/synthetic polymers used in skin regeneration.

3. Synthetic Polymers Used in Skin Regeneration

3.1. Poly(Vinyl Alcohol) (PVOH, PVA, or PVAl)

PVA is a water-soluble and biodegradable biopolymer with a molecular weight ranging from 20,000 to 200,000 D, a glass transition temperature of about 85 °C, a melting temperature of 200 °C, and degradation and biodegradation dependent on factors such as the degree of hydrolysis, temperature, medium, and microorganism used during experiments. It is produced from either the polymerization of vinyl acetate or the radical polymerization of vinyl formate, vinyl pivalate, and vinyl trifluoroacetate [90]. PVA has been extensively used as a polymeric matrix for the fabrication of polymers for skin and tissue repair, including hydrogels [91,92], membranes [93], xerogels [94], fibers [95,96], electrospun fiber mats [97], porous scaffolds, and 3D-printed scaffolds due to its biodegradable, hydrophilic, and biocompatible nature [98,99]. Its great potential in regenerative medicine lies in its low cytotoxicity, high water absorption, favorable mechanical properties, and biocompatibility.

Advantages and Limitations

In spite of its very versatile nature, PVA's major drawbacks lie in its low recyclability and biodegradability [100]. Additionally, due to its hydrophilic nature, it can easily pollute waterways. Composite polymers based on PVA exhibit higher water uptake, so they are often combined with other polymers or crosslinked [100]. One of the major disadvantages also relates to its release of few cytotoxic subproducts during biodegradation, which negatively impacts cell interactions [101,102].

3.2. Polyglycolide or Poly(Glycolic Acid) (PGA)

PGA is a synthetic polymer with good biodegradability and biocompatibility widely used in biomedical applications and skin repair and regeneration. It is composed of a simple linear aliphatic polyester and forms a crystalline or semicrystalline polymer with very good physicochemical properties, such as fast degradation, good barrier properties, high tensile modulus (12.5 GPa), moderate melting point (Tm) > 200 °C, and a glass transition

temperature (Tg) of 40 °C [103]. Indeed, PGA can be completely biodegraded in less than 12 months under physiological conditions, producing glycolic acid as a degradation subproduct [104]. To date, it has been used to fabricate different types of 3D composite materials and matrices for tissue and skin regeneration using techniques such as extrusion, compression molding, injection molding, and solvent casting [105]. Among the different materials fabricated so far for application in skin and tissue engineering are injectable photopolymerized hydrogel [106], core–shell electrospun nanofibers [107], hydrogels [108], branched scaffolds [109], and layered biocomposites [110].

Advantages and Limitations

Amongst its limitations, PGA possesses elevated costs. However, the development of China's coal-to-ethylene glycol industry has made possible the production of PGA at a large scale using dimethyl oxalate (DMO), providing more affordable prices. During biodegradation, PGA produces glycolic acid as a subproduct, which has been widely linked to inflammatory responses and is a major disadvantage in skin regeneration therapies. PGA is only soluble in organic solvents (often expensive), which is a drawback from a sustainability point of view. Alone, PGA exhibits insufficient toughness and brittle features [103]. Indeed, typically, PGA chemical or physical crosslinking is required to meet its intended use in tissue engineering.

3.3. Poly(Lactic Acid) (PLA)

PLA belongs to the aliphatic-polyester-based polymers, also known as polylactides, and is used in the biomedical field due to its biocompatibility, bioabsorbability, thermal stability, and mechanical response. PLA also exists in the form of poly(L-lactic acid) (PLLA), meso-poly(lactic acid), poly(D-lactic acid) (PDLA), and poly(D,L-lactic acid) (PDLLA). PLA is a crystalline polymer with a typical Tg of 60–65 °C, Tm of 175 °C, and tensile strength of 4.8 GPa, which make it a perfect candidate for polymeric wound-healing applications [43]. Several composite polymers based on PLA have been employed to repair damaged skin tissue, including electrospun nanofibers [111,112], hydrogels [113], composite flexible filaments for 3D printing [114], extruded nanofibrils nanocomposites [115], core–shell hybrid electrospun scaffolds [116], bi-layered membranes [117], hybrid porous scaffolds [118], melt-blown nonwoven composites [119], and multifaceted nanohybrid scaffolds [120].

Advantages and Limitations

Due to its high degree of crystallinity, PLA exhibits poor flexibility, a slow biodegradation rate (could take up to 5 years to be completely reabsorbed by the body), and strong hydrophobicity. The degradation rate, however, can be customized through its association with other biopolymers (PGA, chitosan, CMC, alginate, etc.) [43]. Another major disadvantage of PLA is its brittle nature, but also, it is chemically inert. Thus, any surface/bulk functionalization is a challenging approach [43].

3.4. Poly(Lactide-co-Glycolide) PLGA

PLGA is obtained from the copolymerization of PGA and PLA. It is approved by the Food and Drug Administration (FDA) due to its excellent biodegradability, biocompatibility, and tunable mechanical properties. Its crystallinity and degradation rates can be tuned depending on the ratio of lactide to glycolide used [121]. PLGA degrades via erosion into lactic acid and glycolic acid which are human metabolic and non-toxic or cytotoxic by-products. Typically, within the composition range of 25–75%, PLGA exhibits a hydrolytically unstable and amorphous structure. Its hydrophobic nature does not offer itself a suitable platform for cell adherence, but it can be functionalized or associated with other biopolymeric materials or particles/molecules to improve its biofunctionality. The glass transition temperature (Tg) of these polymers is around 37 °C. Also, PLGA has successfully been used for decades in several skin and tissue engineering applications as nanoparticles [122,123], microparticles [124], electrospun co-axial fibers [125], bilayer electrospun membranes [126],

nanosuspensions [127], thermogel dressing [128], hydrogels [129], microspheres [130], composite biofilms [131] and nanocomposites scaffolds [132].

Advantages and Limitations

Hydrophobic PLGA fails to match with extracellular matrix or collagen and thus has poor cellular biocompatibility [133]. It is brittle, but its mechanical properties such as mechanical strength and adhesiveness can be tailored via the inclusion of different biopolymeric materials. It is not soluble in water but also soluble in organic and expensive solvents [134].

3.5. Poly(ε-Caprolactone) (PCL)

PCL belongs to the synthetic polyester family. It has a Tg of 60 °C and a Tm of about 55–60 °C and deserves special attention due to its biocompatibility, biodegradability, non-toxicity, and distinct mechanical properties such as ductility [135]. It is a semi-crystalline aliphatic polyester synthesized via a polymerization reaction using catalysts such as stannous octanoate. It is water-insoluble but soluble in organic solvents [136]. Additionally, it undergoes hydrolytic degradation due to the presence of hydrolytically liable ester linkages with a slow rate of degradation for up to 2–3 years. Due to their versatility, PCL-based biocomposites can be fabricated into different shapes and sizes, which can mimic the properties of extracellular matrix (ECM) but can also activate the fibroblast growth factors and support the cellular migration, adhesion, proliferation, and angiogenesis processes. Several composite polymers based on PCL have been employed to date, aiming to repair skin tissues including core–shell electrospun nanofibers [137], conductive biomimetic bilayer fibrous scaffold [138], hydrogels [139], 3D-printed dressings [140], nanocomposite sponges [141], scratched nano grooves films [142], air-jet spinning film [143], injectable thermosensitive hydrogel [144], and decellularized-extracellular-matrix-decorated PolyHIPE scaffolds [145].

Advantages and Limitations

A major disadvantage of PCL is its lack of intrinsically antimicrobial properties which can be conferred by its association with other polymers or by the addition of bioactive particles/molecules. Additionally, due to their aliphatic nature and their hydrophobic surface, they exhibit naturally poor cell adhesion that can be improved by the addition of other polymeric materials, such as gelatin and collagen among others [135]. PCL alone exhibits a low rate of biodegradation for up to 3 years but can be modulable through its association with other polymers or crosslinkers. Additionally, it is insoluble in water, which often poses serious drawbacks for further processing due to sustainability concerns [136].

3.6. Poly(Vinylpyrrolidone) (PVP)

PVP is approved by the American Food and Drug Administration (FDA) for applications in the biomedical industries as dialysis membranes and contact lenses but also as a binder in pharmaceutical tablet fabrication or as shear thickening additives for toothpaste and other personal care products. Additionally, PVP is used to increase the solubility of drugs in liquid and semi-liquid dosage forms, such as syrups, soft gelatin, and capsules and as an inhibitor of recrystallization [146]. The glass transition Tg value of PVP decreases with a decrease in viscosity and molecular weight from 180 °C to 120 °C [147]. In skin repair and regeneration applications, PVP is widely used due to its interesting physicochemical and biological properties, such as its biocompatibility, hemocompatibility, biodegradability, low cytotoxicity, and water solubility at low concentrations as well as good chemical and thermal resistance. Alone, or as biocomposite, it has been used in tissue engineering in the form of hydrogels [148], sponges [149], gels, creams [150], injectable self-healing nanocomposite hydrogels [151], films, electrospun fibers [152], microparticles, nanoparticles, and porous scaffolds.

Advantages and Limitations

The major disadvantages of PVP are related to its poor swelling index, brittle structure, high hygroscopicity, and low degradation rate. Thus, typically, PVP is used alongside other biopolymers, particles and bioactive molecules to confer adequate biological functionality [146]. PVP is soluble in water but at lower weight content. Therefore, higher-PVP-content solutions will require elevated temperatures or the use of hazardous organic solvents, and thus with several energetic, cost and environmental associated limitations.

4. Types of Cells Used as In Vitro Models for Skin Regeneration

The ability of polymers in skin regeneration is successfully evidenced by in vitro culture models using different types of skin cells. The most studied skin cells are human neonatal dermal fibroblasts, neonatal epidermal keratinocytes [153], HaCaT cells [154–156], epidermal pluripotent stem cells [157], foreskin-derived keratinocytes [158], dermal fibroblasts [159], keratinocyte stem cells [160], angiogenic endothelial progenitor cells [161], hair follicle stem cells [162], adipose-tissue-derived mesenchymal stem cells [163], and bone-marrow-derived mesenchymal stem cells [164].

Kim et al. investigated the capability of skin-derived extracellular matrix (S-dECM) bio-ink for 3D-cell-printing-based skin tissue engineering using human neonatal dermal fibroblasts and human neonatal epidermal keratinocytes [153]. HaCaT cells were used to investigate the skin regenerative properties of cellulose [165,166], chitosan [167], gelatin [166], polyvinylpyrrolidone [152], poly-ε-caprolactone/collagen [168], and hyaluronic acid [169,170]. Several polymers were tested with adipose-tissue-derived or bone-marrow-derived mesenchymal stem cells to prove their skins' regenerative properties [171–175]. Additionally, foreskin-derived keratinocytes are widely accepted as an appropriate model for investigating the skin-regenerative ability of polymers [175–180]. Several authors used keratinocyte stem cells as a skin model to prove their polymers' regenerative properties in the skin [175,176,181,182]. Epidermal pluripotent stem cells are also considered an appropriate model for skin regeneration studies using polymers fabricated in the form of scaffolds, hydrogels, and 3D matrix [183,184].

Currently, many commercial brands are available for in vitro organotypic skin models, such as Human keratinocytes (epiCS (EST-1000) and epiCS-M from CellSystems (Troisdorf, Germany), Epiderm from MatTek Corp. (Ashland, MA, USA), Leiden epidermal skin model (LEM) from Biomimiq (Leiden, The Netherlands), SkinEthic RHE from EpiSkin (Lyon, France), human fibroblasts (3D HSE from MD Biosciences (Zürich, Switzerland) and Fraunhofer IGB (Stuttgart, Germany), AST-2000 from AST-2000, AST-2000 from MatTek Corp. (Ashland, MA, USA)), FDM and FTM from Biomimiq (The Netherlands), Phenion FT from Biomimiq (The Netherlands), StrataTest from Stratatech (Norwalk, CT, USA) and SOR-300-FT from MatTek Corp. (USA) and human melanocytes (epiCS-M from CellSystems (Troisdorf, Germany), MelanoDerm from MatTek Corp. (Ashland, MA, USA), SkinEthic RHPE from SkinEthic RHPE) [185].

5. Signaling Mechanism of Natural Polymers in Skin Regeneration

5.1. Collagen

As an important extracellular matrix component, collagen plays many roles in tissue regeneration. Our studies and other literature reported the possible intrinsic and extrinsic signaling mechanism of collagen in biological cells. Based on empirical evidence, collagen regulates skin regeneration via cellular receptor interactions facilitated by integrins, DDR, glycoprotein VI, osteoclast-associated receptor (OSCAR), LAIR-1, and uPARAP/Endo180 located on the cell surface (Figure 2). By binding with these receptors, collagen in general triggers specific cellular cascade pathways, such as RUNX2, MAPK, ERK, STAT, FcRγ, NF-KB, JNK, ITAM, etc., to regulate biological processes [186,187].

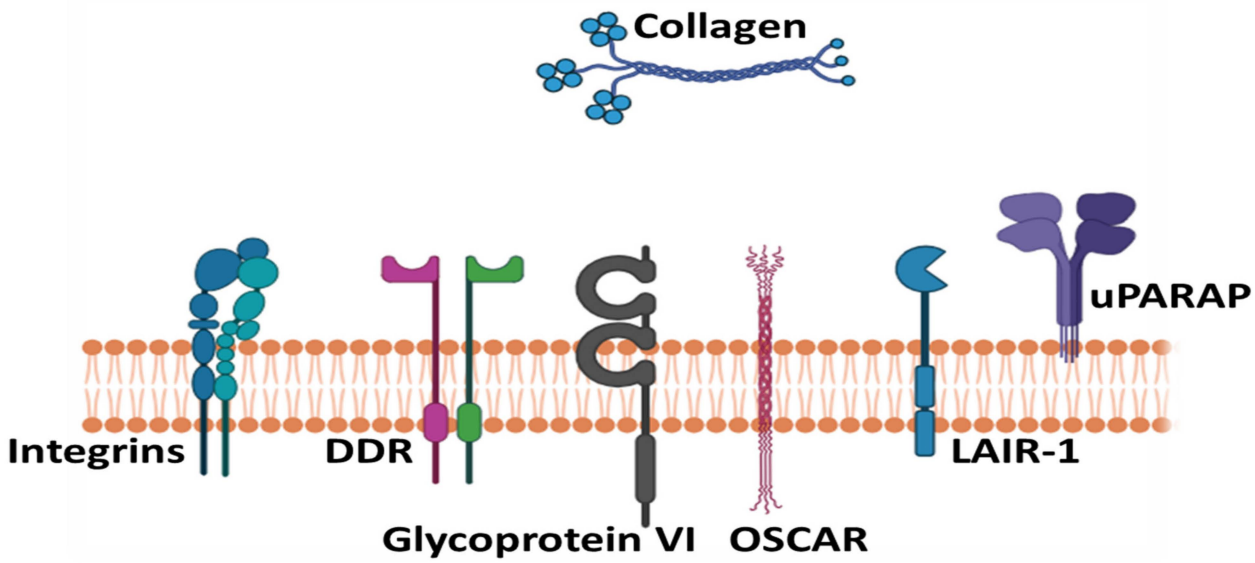

Figure 2. Cell receptor interaction of collagen during skin regeneration.

Collagen regulates many biological processes by activating several intracellular signaling pathways through its peptide sequences. Herein, we summarize the possible ways for collagen to materialize the cell–matrix interaction. Up to now, many collagen-specific cellular receptors have been identified, such as collagen activating the Erk1/Erk2 (p44/42) mitogen-activated protein kinase signal transduction pathway to promote cell migration, adhesion, and survival through the interaction of collagen peptide sequence (GFOGER) with several integrins (α1β1, α2β1, α10β1, and α11β1) [188]. During the collagen–integrin binding, "outside-in" signaling transmits several conformational changes, which activates many signaling events. Cellular receptors specifically bind with the collagen ligand binding sites of Gly-Pro-Hyp (GPO) repeats, which are crucial for fibril alignment and maintaining external stresses and stiffness of the tissue [189,190]. During the skin-healing process, GPO repeats of collagen specifically bind with G6b-B receptors and leukocyte-associated Ig-like receptors (LAIR-1) expressed on platelets and megakaryocytes to inhibit immune cell differentiation [190]. The two immunoreceptor-tyrosine-based inhibition motifs (ITIMs) of LAIR-1 recruit Src homology phosphatase 1 (SHP-1) and SHP-2 during phosphorylation, which then dephosphorylates Syk, Zap70, and PLCγ, inhibiting the stimulation of protein kinases by the immunoreceptor-tyrosine-based activation motif (ITAM) [191,192].

During the recognition of damaged epithelium, collagen fragments activate intracellular signals by interacting with inhibitory platelet receptors, G6b-B [193,194]. G6b-B consists of an immunoreceptor-tyrosine-based switch motif (ITSM) and ITIM, which influence the activity of ITAM through adaptor molecules [194]. ITAM-mediated signaling via the binding of collagen with immunoglobulin (Ig) superfamily member glycoprotein VI (GPVI) is interfered with by G6b-B [195].

The interaction between collagen and stimulatory receptors, OSCAR, is achieved by the GPOGPX′GFX′ sequence of the triple-helical peptide. The activation of OSCAR by the collagen sequence triggers the nuclear factor of activated T-cells (NFAT), which signals via the CD3ζ cytoplasmic signaling domain [196].

During wound healing, collagen fragments activate with the GPVI receptor in coagulation, and the activated GPVI initiates the binding of ITAM-containing FcR-γ chains with Syk [197]. This intracellular signal activates Syk proteins and tyrosine phosphorylation, and this downstream signaling mechanism is dependent on the intact fibrillar conformation of collagen. Similar to OSCAR, GPVI also specifically binds with GPO repeats of collagen in order to initiate inside-out signaling of integrins during platelet adhesion and aggregation [197].

Another collagen-binding receptor, urokinase plasminogen activator receptor-associated protein (uPARAP/Endo180, FN-II domain), specifically binds to collagen GXY triplet motifs. These motifs are exposed, recognized, and internalized from an unfolded collagen triple helix during the degradation of collagen in tissue remodeling [198,199]. The glycosylated motifs of basement membrane collagen IV also interact with the lectin domain of uPARAP/Endo180, modulating the endocytic efficiency [199]. The distribution of glycosylation motifs, especially monoglycosylated (Gal-Hyl) and diglycosylated (Glc-Gal-Hyl) motifs, increased the thermal stability of collagen and reduced rates of digestion by mammalian collagenase [200].

It is opined that the ON/OFF signaling mechanism of collagen is controlled by a stabilization switch such as phosphorylation/dephosphorylation [201]. Collagen fibrils (I, II, and III fibrils) interact with discoidin domain receptors 1 and 2 (DDR1/2) and activate a unique activation pathway, tyrosine auto-phosphorylation, to trigger receptor internalization in order to promote cell proliferation, migration, and survival [202–204].

Collagen also modulates the ligand–receptor activity and increases TGFβ signaling through binding with growth factors, such as transforming growth factor-β (TGFβ) in skin regeneration [205]. The interaction of collagen fibers with TGFβ accelerates the organization of the intracellular actomyosin network and ECM stiffness in epithelial cells.

Similar to collagen, gelatin retains the active motifs GxOGER and RGD sequences, which are recognized by integrins αvβ3 and α5β1 to trigger ERK signaling and regulate cell adhesion and mechanosensing [206].

5.2. Chitosan

The mode of interaction of chitosan with cell receptors is affected by the molecular weight of chitosan (Figure 3). For instance, a lower radius of gyration low-MW chitosan of less than 6 nm directly permeates the cell membrane through pores and enters cells to initiate intracellular interactions. A radius of gyration of low-MW chitosan of less than 50 nm facilitates the engulfing process through endocytosis, and a radius of gyration of chitosan greater than 350 nm initiates the interaction of protein receptors on the cell membrane [207]. The chitosan monomer (N-acetyl-D-glucosamine/1,4-D-glucosamine) cannot interact with the cell as a polycation due to a lack of molecular chain despite it being able to enter the cell [207].

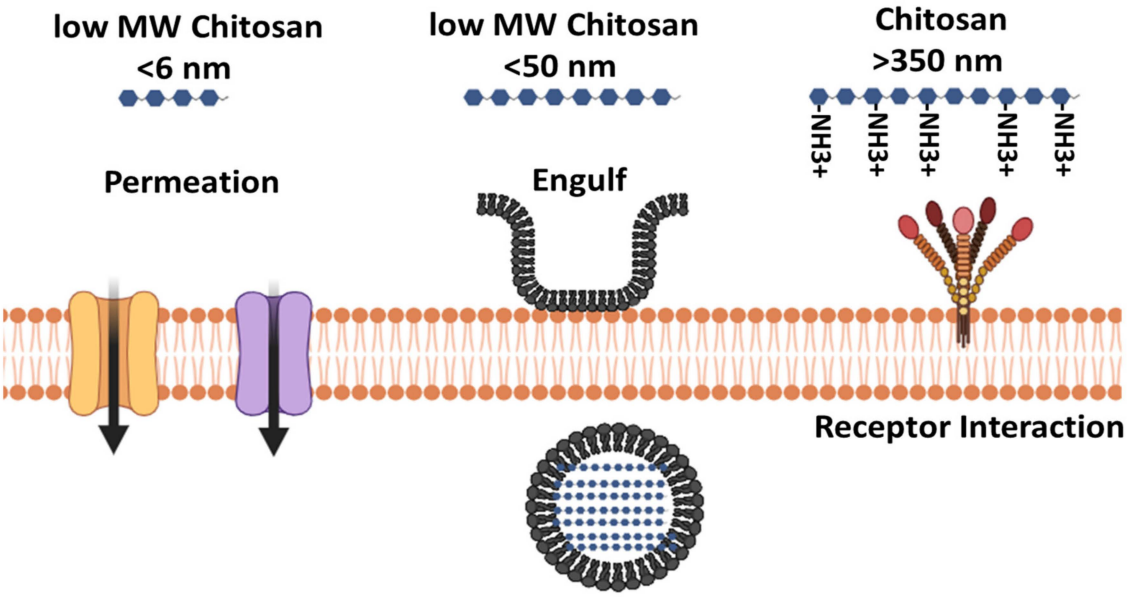

Figure 3. Cell receptor interaction of chitosan during skin regeneration.

As a linear chain, the low-MW chitosan usually exposes more functional -NH3+ groups, which facilitates interaction with the target organism [208]. On the other hand, the

higher-MW chitosan (more than 600 backbone atoms) is usually wrapped around the -NH3+ groups to form a coil structure, which impairs interaction with the target organism [207]. In general, high-MW chitosan is more effective compared to low-MW chitosan due to its intact structure and stability, however, reports claimed that low-MW chitosan had better biological activity than high-MW chitosan. This controversy could be explained by the above interaction mechanism (more functional group exposed in low MW chitosan) and also the polycationic behavior of low-MW chitosan.

The chitosan stimulates STAT3 tyrosine phosphorylation, interleukin-22, and interleukin-6 secretion by interacting with cellular receptors, such as secreted C-type lectin (regenerating islet-derived protein 3-alpha (RegIIIA)) [12]. It has been reported that chitin activates several signaling pathways, such as protein kinase B (AKT), Janus kinase/signal transducer and activator of transcription protein (JAK/STAT1), and extracellular-signal-regulated kinase (ERK) through interacting with a member of the beta-galactoside-binding protein galectin-3, which is responsible for cell–cell adhesion and cell–matrix interactions [209,210]. Other studies also claimed that chitosan maintains the levels of cytokines and chemokines by interacting with fibrinogen-C-domain-containing protein 1 (FIBCD1), toll-like receptor/myeloid differentiation primary response 88 (TLR/MyD88) and NK cell receptor protein 1 (NKR-P1) [192,211,212]. Chitosan modulates nuclear factor kappa-B (NF-κB) signaling by inducing IL-10 secretion [213,214].

5.3. Alginate

Alginate is derived from algae or seaweed and is mainly used in drug-delivery devices. The functional unit of alginate could interact with toll-like receptor (TLR) 4, which is an important polysaccharide receptor (Figure 4A). The interaction of alginate with TLR4 is dependent on the molecular weight, monosaccharide composition, glycosidic bonds, functional groups, and branched-chain structure of polysaccharides. [215–218].

The identified cellular receptors for glucuronoxylomannan are CD14, CD18, TLR2, and TLR4 (cryptococcal glucuronoxylomannan interferes with neutrophil rolling on the endothelium) [219,220]. The interaction of glucuronoxylomannan with macrophage receptors triggers the activation of NF-kB [218]. The interaction of alginate with cellular receptors triggers growth factor release (TGF-β3 and BMP-2) and accelerates the differentiation of mesenchymal stem cells [221,222]. During infection in the skin, alginate binds with macrophage receptors to activate macrophage-like cells (RAW264.7) through the NF-κB pathway [223].

5.4. Fibroin

Fibroin induces cell proliferation and differentiation by activating intracellular pathways. Fibroin is recognized by the cellular receptors of α5β1 integrin (Figure 4B) at NINDFDED and VITTDSDGNE peptide sequences in order to upregulate the receptor activation of nuclear factor κB ligand (RANKL), JNK 1/2 kinases, ERK1/2, NF-κBp65,c-Jun, and c-Jun protein phosphorylation [224–226].

5.5. Hyaluronan

Hyaluronan specifically interacts with cell surface receptors such as HA-mediated motility (RHAMM) and the cluster of differentiation-44 (CD44) (Figure 4C) [39]. Both receptors are composed of essential amino acid residue, arginine or lysine, and other non-acidic amino acids, which link to the disaccharide units of N-acetyl glucosamine and glucuronic acid of hyaluronan [227]. The critical events in morphogenesis, such as cell locomotion and proliferation, are controlled by interactions between hyaluronan and the cell surface receptors CD44 and RHAMM [227]. The interaction of hyaluronan–CD44 activates downstream signaling pathways, Rho and Rac1 GTPases, leading to erbB2 tyrosine kinase activation [228], reorganization of the actin cytoskeleton [229], and cell proliferation through NF-κB [230] and src-related tyrosine kinases [231]. The activation of RHAMM

triggers a protein tyrosine kinase signal transduction pathway (pp60c-src), leading to focal adhesions for RHAMM-associated mediated cell motility [232].

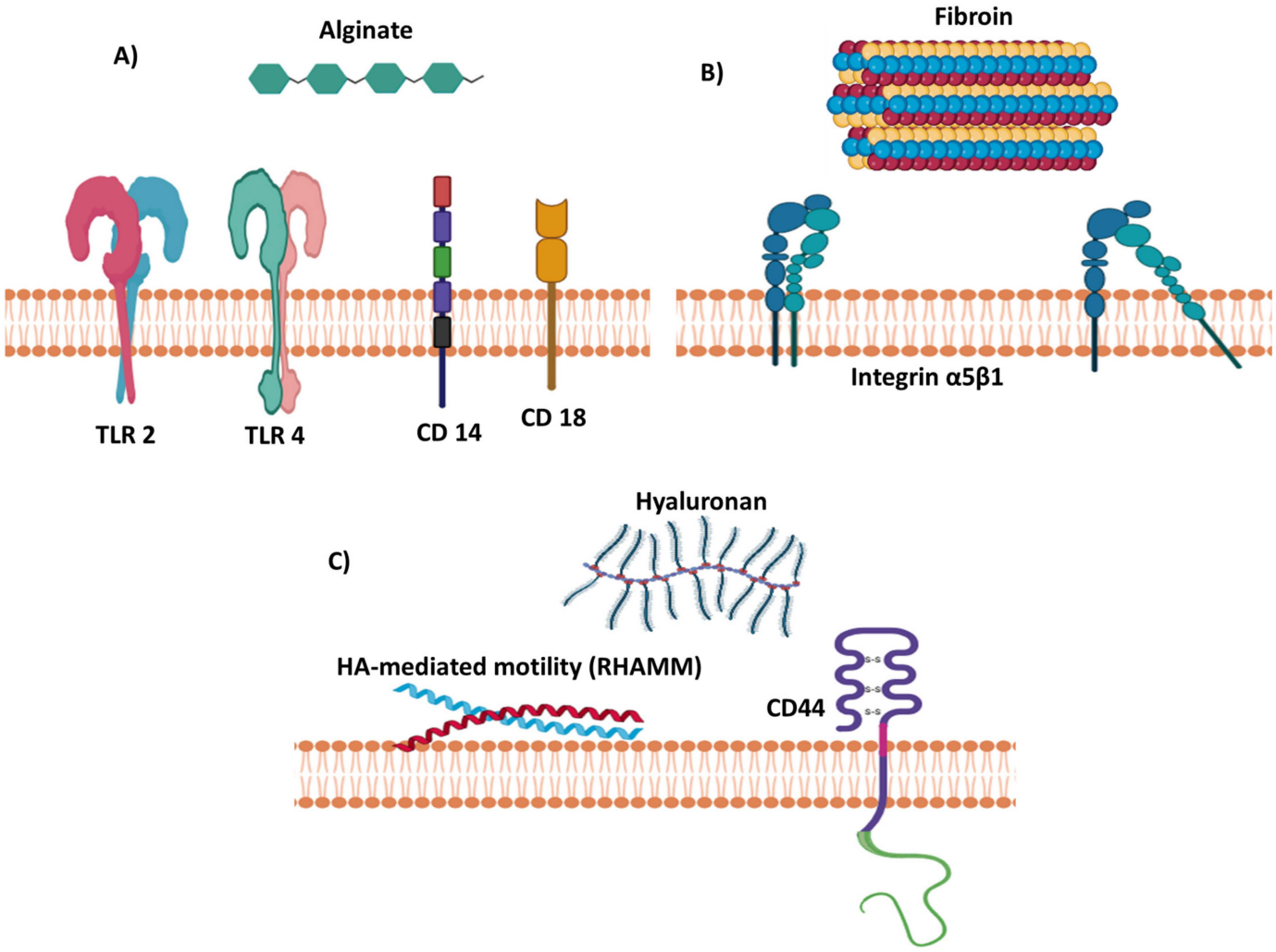

Figure 4. Cell receptor interaction of alginate (**A**), fibroin (**B**), and hyaluronan (**C**) during skin regeneration.

As discussed before, the molecular weight of hyaluronan plays an important role in matrix recognition and biological function [233]. By interacting with RHAMM and CD44 cellular receptors, the lower-MW hyaluronan triggers the TLR-4 signaling pathway through phosphorylation of nuclear translocation of NF-κB and p38/p42/p44 MAP-kinases [234,235]. At the same time, the high-MW hyaluronan promotes an anti-inflammatory effect by interfering with interferon α2β (IFNα2β), brain-derived neurotrophic factor, nerve growth factor, and IL1-β receptor signaling pathways and downregulating IFNα expression [38,236,237].

5.6. Fibrin

Fibrin promotes the transendothelial migration of inflammatory cells to the endothelium by interacting with cellular receptors such as the endothelial cell receptor ICAM-1 and the leukocyte receptor Mac-1 (αMβ2 integrin) (Figure 5) [238,239]. Additionally, by interacting with the endothelial cell receptor VE-cadherin, fibrin presents leukocytes to the endothelium and promotes capillary tube formation by the endothelial cell monolayer. Hence, the interaction of fibrin with VE-cadherin modulates both fibrin-dependent inflammation and angiogenesis [240,241]. More specifically, the functional NH_2-terminal portions of fibrin βN-domains containing His16 and Agr17 are essential for high-affinity interac-

tion with VE-cadherin [239]. The cell surface integrin receptors and non-integrin (e.g., VE-Cadherin, I-CAM-1, P-selectin, and GPI-bα) receptors play a critical role in the interaction of fibrin, and α- and β-subunits of transmembrane cell adhesion molecules bind fibrin during skin regeneration [241–243]. Additionally, fibrin is reported to bind with αIIbβ3 on platelets, αvβ3, αvβ5, and α5β1 on EC and with αMβ2 on leukocytes [238,243,244]. The fibrin's α-chain contains RGD sequences at positions Aα95–97 and Aα572–574, which could bind with the αvβ3-integrin in epithelial cells [243].

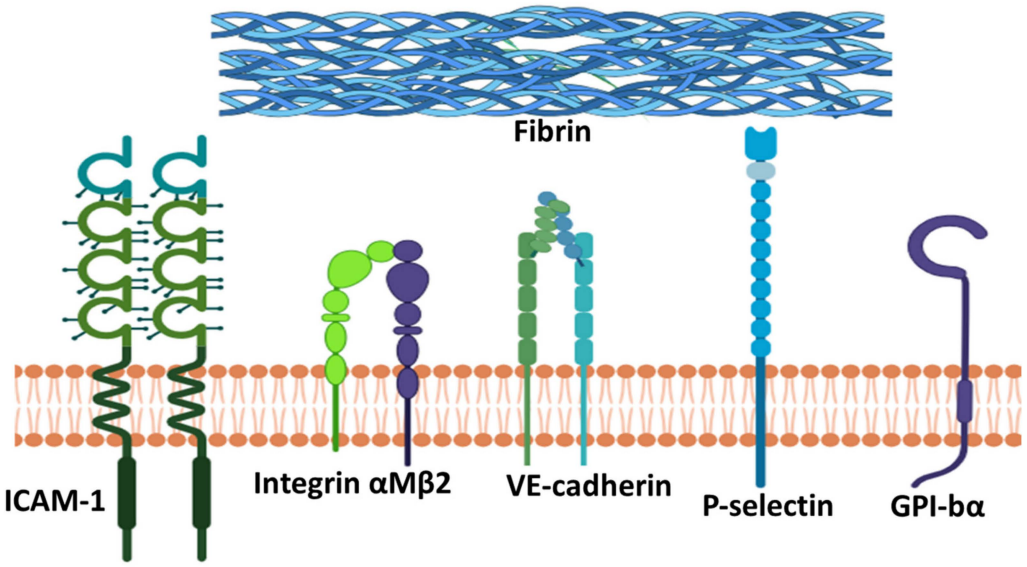

Figure 5. Cell receptor interaction of fibrin during skin regeneration.

5.7. Cellulose

Notch receptors play a major role in cellulose interaction in cells [245]. Ultimately, the monomer of cellulose, glucose is transported in keratinocytes mediated through Glut1, l-type amino acid transporter (LAT)1, cationic amino acid transporters (CATs), G-protein-coupled receptors, and heterodimer of T1R3 and CaSR (Figure 6) [246–249].

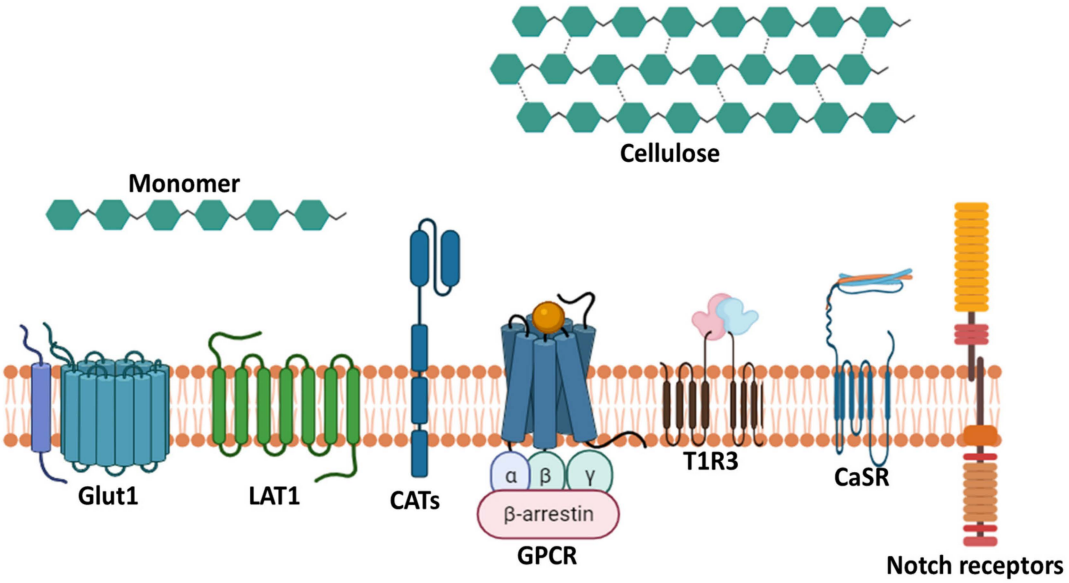

Figure 6. Cell receptor interaction of cellulose during skin regeneration.

6. Signaling Mechanism of Synthetic Polymers in Skin Regeneration

In general, the receptor interaction of synthetic polymers lies in only two mechanisms. (1) In most cases, the synthetic polymers having cationic monomers interact with negatively charged cell membrane surface through electrostatic interaction [250]. (2) Synthetic polymers having anionic monomers do not interact with the cell surface, which needs additional functional materials for its biological activity. The main drawback of synthetic polymers used in biological applications is that the actual interaction between synthetic polymers and the cell surface has not been studied systematically yet. This is because of the lack of specific molecular and cellular interacting sites in cell membranes for most synthetic polymers. Due to this, they are adsorbed non-specifically from their surrounding environment [251]. Even though some of the literature has discussed the membrane receptor mechanism of synthetic materials, most of the reports discussed either the receptor activation of composite polymers (two or three polymers together) or surface-functionalized synthetic materials with fibronectin or collagen [252], not a single synthetic polymer. Interestingly, Teramura et al. investigated how the interaction modes affect the stability and dynamics of synthetic polymers such as PEG–lipids, alkyl/carboxylated PVA, PEG–NHS, and poly(ethylene imine) on the cell surface. Their study concluded that PVA-alkyl and PEG-lipids interact with cell membranes, specifically the lipid bilayer, through hydrophobic interaction. PEG–NHS anchored the membrane proteins on the surface of cells through covalent bonds, and carboxy PVA and poly(ethylene imine) anchored with the cell membrane in different modes through electrostatic interactions. PEG chains seem to interact with sugar chains on the cell surface through hydrogen bonding to induce clustering and destabilization of the lipid bilayer membrane. Another study reported that PEG was covalently bound to the surface of red blood cells through cyanuric chloride coupling [253].

Poly(ethylene imine) and carboxylated PVA interact. The fibrillar adhesions and fibrillogenesis of PVA were altered by the interaction between the cell receptors paxillin and α5 integrin [254]. It is also opined that PVA binds growth factor receptors, such as fibroblast growth factor-2 [255]. A detailed mechanism of PVA interaction with cell membrane was reported by Teramura et al. 2008, and they opined that PVA carrying alkyl side chains (PVA–alkyl) could initiate hydrophobic interactions in order to anchor the membrane lipid bilayer of cells and PVA with a carboxyl group (PVA–COOH) and could interact electrostatically with the cell membrane [250]. Another scenario of cell–polymer interaction depends on the formation of protein layers on the surface of polymers. For instance, synthetic polymers such as PET, PVA, and PDMS are strongly bound to serum proteins, such as complement C4, serum amyloid P, albumin, transferrin, and immunoglobulins [256]. Overall, based on the available literature, synthetic materials interact with cell membranes in three possible ways: covalent binding, hydrophobic interactions, and electrostatic/ionic interactions [12] (Figure 7).

In summary, Table 1 shows the composite polymers used for wound healing and skin/tissue regeneration reported recently, including the type of material fabricated, targeted application, processing technique, and their main biological functionality and characterization.

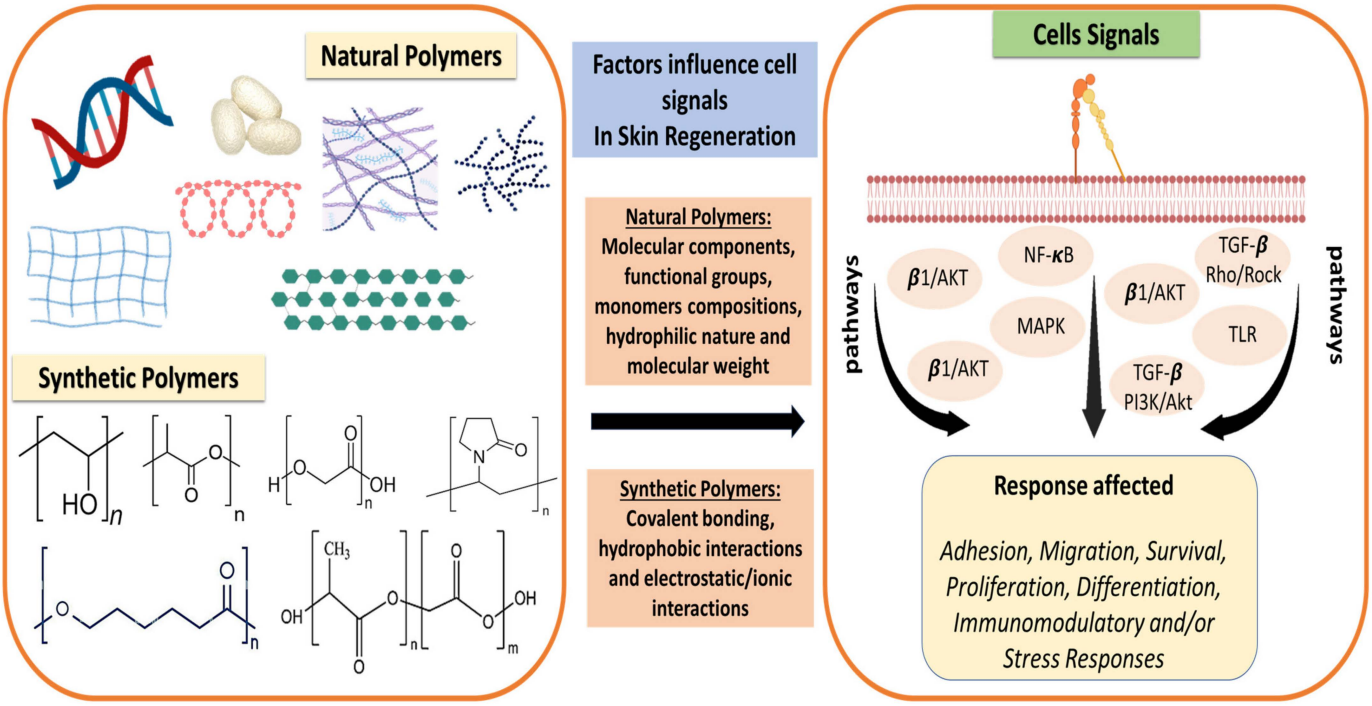

Figure 7. Signaling mechanism of natural and synthetic polymers in skin regeneration.

Table 1. Natural and synthetic composites polymers for wound-healing and skin/tissue applications.

Type of Polymer	Fabrication Technique and Type of Material	Main Results and Biological Characterization	Reference
PVA, collagen, Nigella sativa and chitosan	Electrospun nano hybrid scaffolds for skin regeneration	In vitro antibacterial properties against *S. aureus* and *E. coli* and favorable in vivo biocompatibility using rabbit models	[257]
Cellulose/collagen/silk fibroin	Highly interconnected 3D hybrid matrix aerogel. Freeze drying for wound healing	Excellent biocompatibility and cell proliferation using NIH 3T3 fibroblast and MG-63 osteoblast cells	[258]
PVA/egg white protein/graphene oxide	Electrospun nano hybrid scaffolds	Enhanced in vitro cell adhesion, migration, survival and proliferation of human dermal fibroblasts (HDFs) and human umbilical vein endothelial cells (HUVECs). In vivo, biocompatibility with SD rats showed that the wound dressing	[259]
PVA, MXene/CuS, and polydopamine (PDA)	Hydrogel–polymer blend to treat wound	In vitro antibacterial properties against *S. aureus* and *E. coli* and enhanced in vitro adhesion and proliferation using L929 cells, also in vivo wound healing improvement using male mice models	[260]
PVA/polyaniline/chitosan	Conductive hybrid scaffold based on nanoparticles. Films fabricated by solution casting	enhanced in vitro antibacterial properties against gram-positive (*E. faecalis*, *S. aureus*) and gram-negative (*E. coli*, *S. typhi*), and in vitro hemolytic assay value less than 2% applicable for skin repair	[261]
Poly ether ether ketone (PEEK) with resveratrol	Electrospun two-dimensional (2D) nanofibrous scaffolds	Improved antibacterial and antifungal activity using Gram-positive *S. aureus* and *S. faecalis*, gram-negative *E. coli* and *P. aeruginosa* and *C. albicans* as fungal strain. Enhanced in vitro biocompatibility: adhesion and proliferation using skin keratinocyte (HaCaT) and in vivo wound healing using female Wistar rats	[262]

Table 1. *Cont.*

Type of Polymer	Fabrication Technique and Type of Material	Main Results and Biological Characterization	Reference
PCL and collagen	Electrospun fiber mats using dual pumps. Free-scare wound healing	Excellent in vitro adhesion, proliferation, and low cytotoxicity using PCS-201 (human dermal fibroblast, HDF) and HaCaT (keratinocytes) and in vivo wound healing efficacy using the excision model of Sprague–Dawley rats.	[263]
Cellulose acetate/ethylenediaminetetraacetic (EDTA)-dianhydride and propolis ethanolic	Lyophilized hydrogels to treat second-degree burns	Excellent antimicrobial and anti-inflammatory properties. Also, hydrogels Influence the in vivo wound healing using healthy SPF male Wistar rats	[264]
Gelatin/N-(2-Hydroxyethyl)acrylamide (HEAA)/Poly(ethylene glycol) diacrylate (PEGDA)	Self-healable composite hydrogels fabricated using UV initiators to increase collagen deposition and vascular regeneration	Excellent antimicrobial (antifouling) response using gram-negative *E. coli* and gram-positive *S. aureus.* Enhanced in vitro proliferation using L929 cells and in vivo hemolysis (blood), hemostasis (conducted using rat liver hemorrhage model), and wound healing efficacy using Sprague–Dawley rat model	[265]
PCL/Chitosan/poly(ethylene oxide)	Electrospun 3D nanofibrous scaffolds decorated with CS flakes fabricated using simultaneous deposition horizontal/vertical improved vascularization	Enhanced biocompatibility was demonstrated using in vitro cell culture with human dermal fibroblasts (HFFF2) cells. Additionally, the addition of CS flakes lowers both the adhesion and the proliferation of HFFF2	[266]
PVA/quercetin	Nanosized PVA/quercetin xerogel films fabricated using a transverse electrospray deposition device for wound dressing	Improved antibacterial activity against *E. coli* and *S. aureus*. Improved protein adhesion. Improved in vitro and in vivo biocompatibility using HaCaT cells and male Kunming mice as biological models, respectively	[94]
Collagen Type II/Clay nanoparticles/Gentamicin	Hydrogels freeze-dried to be applied to skin regeneration	Samples presented a delayed gentamicin release when compared to the collagen–gentamicin sample. Antimicrobial activity against *E. coli* and *S. aureus* was not induced by clays NP. Samples exhibited accepted in vitro viability above 70% compared to control using MG63 cell line (CLS)	[267]
Hydroxyapatite-nanoparticle-thiolated chitosan/Propylene glycol/Polyethylene glycol	Freeze–thawing scaffolds to improve skin tissue regeneration	In silico experiments demonstrate the improved affinity binding effect of the scaffold with epidermal growth factor and glycogen synthase kinase. Excellent in vivo biocompatibility wound healing using albino rats (Wister strain) as biological models	[268]
PVA/Chitosan	Membranes—Freeze-drying	Favorable in vitro biocompatibility using Human Caucasian Fetal Foreskin Fibroblast cell line (HFFF2). Additionally, improvement in cells' morphology and cytoskeletal organization	[93]
PVA/Chitosan	Membranes—Freeze-drying	favorable in vitro biocompatibility using the Human Caucasian Fetal Foreskin Fibroblast cell line (HFFF2). Additionally, improvement in cells' morphology and cytoskeletal organization	[93]

Table 1. *Cont.*

Type of Polymer	Fabrication Technique and Type of Material	Main Results and Biological Characterization	Reference
Iron Oxide Fe_3O_4, silver, gold, and chitosan nanoparticles	Chitosan/metal nanoparticles fabricated using ionotropic gelation strategy for its application in wounded skin management	Good antibacterial activity against E. coli. Good in vitro biocompatibility using mouse embryonic fibroblasts (MEF) cells being the bare CS-NPs the most biocompatible ones. Additionally, good tissue regenerative activity as they promoted the fastest cell migration and improved quantitative wound healing in a fibroblast scratch model in comparison to the bare CS NPs and the CS Au and Ag hybrid nanoparticles	[269]
Pyrrole/hyaluronic acid (HA)/gelatin (GEL)	Cold atmospheric plasma (CAP)-treated hybrid polymeric-based scaffolds fabricated via irradiation-induced polymerization. For improved carriers and regenerating chronic wounds (diabetics)	Scaffolds exhibited improved therapeutics sustained-release/retention effects. Additionally, positive impacts on in vitro wound healing assays using mouse fibroblast cells (L929). Photothermal–hyperthermic effects promoted the expression of heat-shock protein (HSP) with anti-inflammatory properties for boosted restoration of diabetic wounds in vivo demonstrated using Wistar rats as a biological model.	[270]
Chitosan/cellulose/cerium dioxide nanoparticles.	Hydrogels alone and in combination with mesenchymal stem cells to treat acute skin wounds	in vivo comparative study using male Wistar rats. Use of antimicrobial levomekol promotes a slow healing process if wounds had no signs of bacterial contamination. Proven preclinical efficacy of these scaffolds enriched with cerium dioxide nanoparticles, especially in combination with mesenchymal stem cells.	[271]
Polyhydroxybutyrate (PHB), poly(hydroxybutyrate-co-valerate) (PHBV), kappa-carrageenan (KCG), polydioxanone (PDX), fucoidan (FUC + C23), polysucrose (PSuc), poly-l-lactic acid (PLLA), Cellulose, Cellulose Acetate (CA), Nanosilica	Electrospun fibrous scaffolds, and machine learning to treat skin wounds	Prediction of cell–material interactions using machine learning (ML) comparing in vitro biocompatibility using L929 mouse fibroblasts and in vivo biocompatibility using Wistar albino rats model. Fiber diameter and pore diameter emerged as the two physicochemical parameters, which impacted more on the MTT values (viability/cytotoxicity)	[272]
Poly(ethylene glycol), ε-caprolactone (ε-CL)/quaternary ammonium salt/Chitosan	Nanoparticles and hydrogels fabricated via self-assembly and sol-gel, respectively. Accelerated cutaneous wound healing systems	Excellent in vitro antibacterial activity against gram-positive *MRSA* and gram-negative *E. coli*. In vitro cytocompatibility and hemolysis were evaluated on 3T3 cell cultures. In vivo degradation and biocompatibility using a Balb/c mice model.	[273]
Layered perovskite $Na_2La_2Ti_3O_{10}$, $Ag_{0.3}Na_{1.7}La_2Ti_3O_{10}$/Poly(l-Lactide-Co-Glycolide)	Electrospun nanofibrous scaffolds to stimulate tissue self-regeneration and novel wound dressings	Antimicrobial properties against the gram-positive and gram-negative bacteria strains *S. saprophyticus*, *K. pneumoniae*, *P. aeruginosa* and *E. coli.* In vitro biocompatibility was assessed using human dermal fibroblasts (HDF) cells; it was non-cytotoxic and also supports their normal cellular protein expression	[274]
Oxidized hydroxyethyl starch (O-HES)/modified carboxymethyl chitosan (M-CMCS)	Injectable hydrogels composites via polymer blend as accelerating wound healing	In vitro cell biocompatibility using bone marrow MSCs isolated from SD rats. In vivo biocompatibility using Sprague–Dawley rats with full-thickness skin defects. Samples promoted higher wound closure percentage, more granulation tissue formation, faster epithelialization, and decreased collagen deposition	[275]

Table 1. *Cont.*

Type of Polymer	Fabrication Technique and Type of Material	Main Results and Biological Characterization	Reference
Cholesteryl-oligo(lactic acid) (CLA)/PLA	Freeze-dried liquid crystal polymers films for guiding cell fate and tissue regeneration by the spatiotemporal controlling of contact stress between matrix materials and cells	In vitro cell biocompatibility, the phenotypic transformation of cells, and tissue regeneration assessed using mouse embryonic FB (the NIH-3T3 cell line). In vivo biocompatibility was assessed using male Sprague–Dawley rats. The liquid crystal structure induced focal adhesions and activation of the integrin β1/AKT signal pathway, resulting in the phenotypic transformation of fibroblasts to myofibroblasts, collagen secretion, and fast wound filling	[276]
PCL/gelatin/methacryloyl-cephalexin (CEX)	Electrospun nanofibrous mats for wound healing applications	Burst CEX release at the beginning, followed by a sustained release. Antibacterial activity against *E. coli* and *S. aureus*. In vivo biocompatibility using BALB/c mice model demonstrated a wound healing environment with strong antibacterial properties	[277]
TiO_2 nanoparticles loaded O-crosslinked	Microwave-assisted synthesis antibacterial hydrogels for skin regeneration	Antibacterial activity against *E. coli* and *S. aureus*. In vitro degradation in PBS is about 20% in 30 days compared to biodegradation, with lysozyme about 90%. In vitro biocompatibility using mouse L929 fibroblasts enhancing adhesion and proliferation of cells	[278]
Soybean/polyamide-6	Electrospun fiber mats as long-term cutaneous wound coverings	Affinity of peptides enhancement using growth factor attachment. In vitro cytotoxicity, adhesion, and proliferation improved using VERO and 3T3 cells. In vivo biocompatibility using the Wistar albino male model.	[279]

7. Conclusions and Perspectives

Overall, this reviewer disclosed that the receptor interaction of natural materials depends on the molecular components, functional groups, monomer compositions, hydrophilic nature, and molecular weight of polymers used. In most cases, the receptor interaction is more specific for each natural polymer based on the above characteristics and for instance, integrins, DDR, glycoprotein VI, osteoclast-associated receptor (OSCAR), LAIR-1, uPARAP/Endo180 for collagen and gelatin, secreted C-type lectin (regenerating islet-derived protein 3-alpha (RegIIIA)), fibrinogen-C-domain-containing protein 1 (FIBCD1), toll-like receptor/myeloid differentiation primary response 88 (TLR/MyD88) and NK cell receptor protein 1 (NKR-P1) for chitosan, CD14, CD18, TLR2, TLR4 for alginate, α5β1 integrin for fibroin, HA-mediated motility (RHAMM), a cluster of differentiation-44 (CD44) for hyaluronan, endothelial cell receptor ICAM-1 and the leukocyte receptor Mac-1 (αMβ2 integrin), endothelial cell receptor VE-cadherin, fibrin for fibrin, and Notch receptors for cellulose were reported. On the other hand, the synthetic polymers did not facilitate receptor-based interaction like natural polymers and interacted with the cell through three possible ways: covalent binding, hydrophobic interactions, and electrostatic/ionic interactions. All these data summarize the fundamental insights of different polymers used in skin regeneration. However, more studies should be needed to explore the influence of cell-matrix interaction in intracellular downstream signaling cascades. More specifically, the actual interaction of functional groups of synthetic materials with different cellular receptors should be investigated to unknot the major scientific contexts.

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