MINI-REVIEW

Wound dressings for a proteolytic-rich environment

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Abstract Wound dressings have experienced continuous and significant changes over the years based on the knowledge of the biochemical events associated with chronic wounds. The development goes from natural materials used to just cover and conceal the wound to interactive materials that can facilitate the healing process, addressing specific issues in non-healing wounds. These new types of dressings often relate with the proteolytic wound environment and the bacteria load to enhance the healing. Recently, the wound dressing research is focusing on the replacement of synthetic polymers by natural protein materials to delivery bioactive agents to the wounds. This article provides an overview on the novel protein-based wound dressings such as silk fibroin keratin and elastin. The improved properties of these dressings, like the release of antibiotics and growth factors, are discussed. The different types of wounds and the effective parameters of healing process will be reviewed.

Keywords Wound healing · Silk fibroin · Collagen · Elastin · Keratin

Introduction

In the past, traditional dressings such as plant fibers, honey and animal fat were used to cover the wound, keeping it dry by allowing the evaporation of wound exudate and preventing the entry of harmful bacteria into the wound. Nowadays, the development of new biopolymers and fabrication techniques creates wound dressings with improved properties that enhance the healing process. Effective wound management requires the understanding of the type of wound and healing process. The physical, mechanical and chemical properties of the dressing must also be taken into consideration. The new biomaterials to be applied as wound dressings should create a moist environment around the wound, effective oxygen circulation, cellular guidance and low bacterial load. This review discusses the basic principles of wound healing, type of wounds and the type of wound dressings. An overview will be given on the properties of fibrous proteins and their characteristics as wound dressings.

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Wounds and wound healing process

A wound, according to the Wound Healing Society, is the result of "disruption of normal anatomic structure and function" (Lazarus et al. 1994). Based on the nature of the repair process, wounds can be classified in acute wounds and chronic wounds. Acute wounds usually heal completely within 8–12 weeks with minimal scarring (Nicholas 2002). The primary causes of acute wounds include mechanical injuries and burns.

Chronic wounds fail to heal in the expected time frame and persist beyond 12 weeks, with the possibility to reoccur (Harding et al. 2002). A chronic wound does not heal properly because the orderly sequence of events is disrupted at one or more stages of the healing. The factors that inhibited or negatively influence the healing can be divided into systemic and local (Table 1). A chronic wound is usually a permanent inflammatory state comprising a high and constant proteolytic activity. This will diminish the recognition and subsequent removal of cells by macro-

Table 1 Factors that inhibit wound healing (Enoch and Leaper 2008; Thomas et al. 2010)

Local factors	Systemic factors
Scalds and burns (physical and chemical)	Advanced age and immobility
Local pressure	Obesity
Compromised vascular perfusion (arterial, venous or mixed)	Malnutrition and nutritional deficiencies
Neurologic defects	Systemic malignancy and terminal illness
Inadequate blood supply	Immunodeficiency
Poor venous drainage	Trauma (initial or repetitive)
Foreign body and foreign body responses	Chemotherapy and radiotherapy
Infection	Immunosuppressive drugs, corticosteroids and anticoagulants
Excess local mobility	Psychosocial stress
Underlying osteomyelitis	Systemic diseases (diabetes, rheumatoid arthritis, connective tissue diseases, metabolic diseases)
Malignant transformation (Marjolin's ulcer)	Inherited neutrophil disorders
	Impaired macrophage activity

phages promoting a necrotic disintegration. Chronic wounds include decubitus wounds (pressure sores); venous, arterial and diabetic foot ulcers; and wounds due to autoimmune disease. Although chronic wounds are a clinical and economic burden, there has been little consensus on how to diagnose and treat them (Kuehn 2007).

Principles of wound healing

Wound healing is a specific biological process related to the general phenomenon of growth and tissue regeneration. There are several reports describing the various biological and physiological stages of healing (Boateng et al. 2008; Queen et al. 2004; Strodtbeck 2001). The wound healing process can be summarized into five independent and overlapping stages, including hemostasis, inflammation, migration, proliferation and maturation (Fig. 1). The healing process is not linear and can progress forward and backwards through the phases depending on various factors.

Hemostasis and inflammation occurs soon after the damage of the skin, which is often accompanied by bleeding. This activates hemostasis through fibrinogen that leads to the coagulation of exudates (blood without cells and platelets) and, together with the formation of a fibrin network, produces a clot in the wound that stops the bleeding and provides a temporary matrix for cellular migration. Inflammation occurs almost simultaneously with hemostasis, from within a few minutes to 24 h and lasts for about 3 days, involving the infiltration of the wound with polymorphonuclear leukocytes (neutrophil granulocytes) whose main function is to minimize bacterial contamination of the wound preventing infection. At later stages of inflammation, macrophages are the most important cells being the principal producer of growth factors responsible for the proliferation.

Migration and *proliferation* involves the movement of epithelial cells and fibroblasts to the injured area to replace damaged and lost tissue. These cells regenerate from the margins, rapidly growing over the wound under the clot followed by deposition of the extracellular matrix. With the progression of the proliferative phase, the temporary fibrin/fibronectin matrix is replaced by the newly formed granulation tissue and collagen synthesis.

Maturation is also named the remodeling phase and involves the formation of cellular connective tissue and strengthening of the new epithelium, which determines the nature of the final scar. There is continuous synthesis and breakdown of collagen as the extracellular matrix is constantly remodeled, equilibrating to a steady state after approximately 21 days after wounding.

The most important cells involved in the various steps of wound healing are summarized in Table 2.

Proteolytic and microbiological environment of wounds

Wounds, acute or chronic, are characterized by the production of fluid, exudate, which is a key component in all stages of wound healing, irrigating the wound continuously and keeping it moist (Gray and White 2004). Exudate supplies nutrients and leukocytes to the wound, which helps control bacteria and infection. In chronic wounds, there is excessive amount of exudate that can cause maceration of healthy tissue around the wound (Cutting and White 2002). In addition, exudate from chronic wounds differs from that of acute wounds with relatively higher levels of tissue destructive proteases, namely metalloproteinases (MMPs)

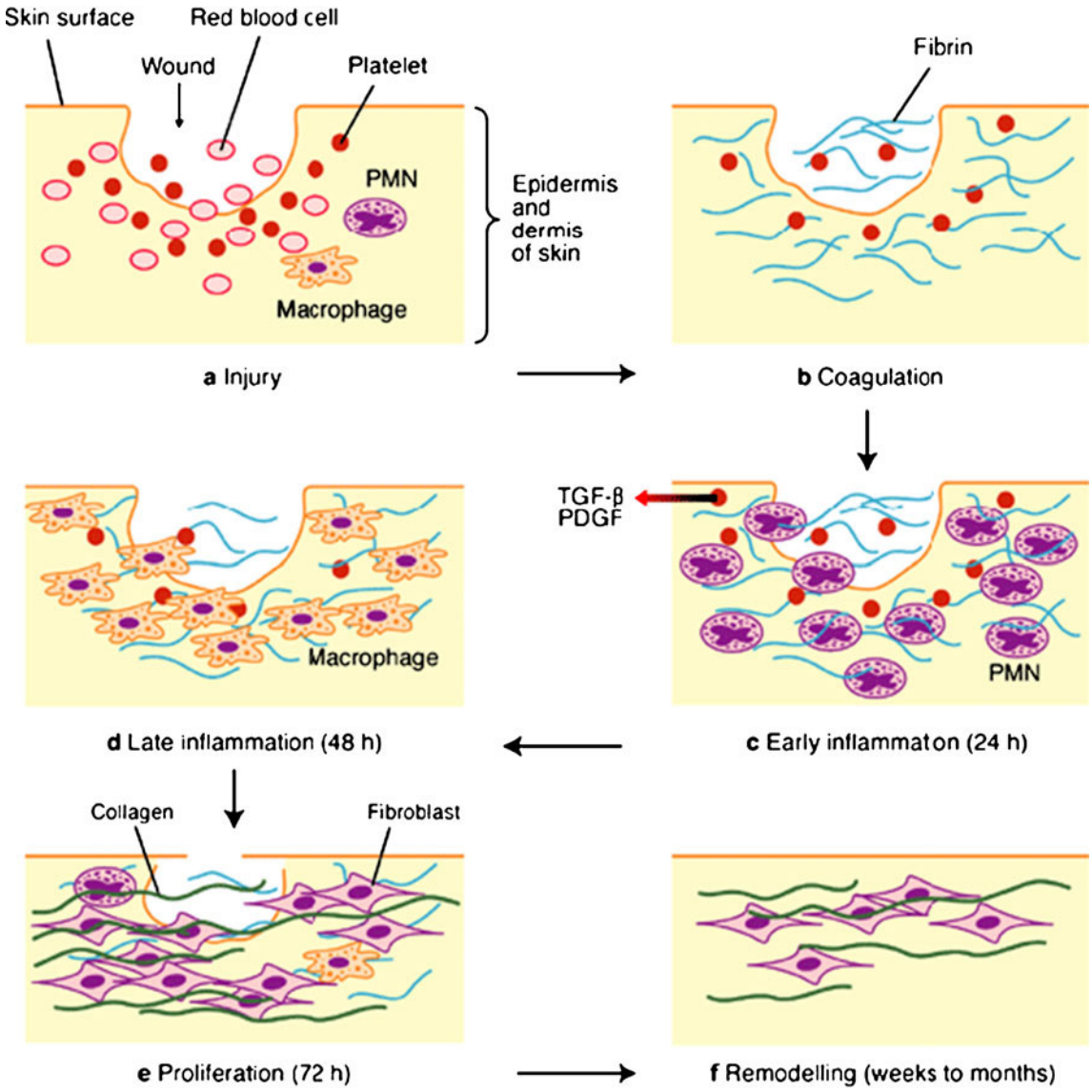

Fig. 1 Phases of cutaneous wound healing (adapted from Strodtbeck 2001)

and polymorphonuclear elastase (Chen et al. 1992). Exudate obtained from chronic wounds has been shown to contain human neutrophil elastase, cathepsin G, urokinase-type plasminogen activator and gelatinase (MMP-9; Chen et al. 1992; Cutting and White 2002).

A wound often provides a moist, warm and nutritious environment to microbial colonization and proliferation. The number and diversity of microorganisms will depend on the type of wound, depth, location and the antimicrobial efficacy of the host immune response. Wound colonization is most frequently polymicrobial (Bowler 1998; Bowler and Davies 1999; Bowler et al. 2001), involving numerous microorganisms that are potentially pathogenic, which may lead to infection. When infection is present, the wound fails to heal, and there is increased trauma to the patient and increased treatment costs. Infection should be considered if one of the following is present: pyrexia, increased pain, increasing erythema of surrounding skin, lymphangitis and rapid increase in wound size (Douglas and Simpson 1995). Nevertheless, since chronic wounds may not always display the classic symptoms of infection, signs such as serous exudate plus concurrent inflammation, delayed healing, discoloration of granulation tissue, friable granulation tissue, foul odor and wound breakdown should also be used to identify infection (Gardner et al. 2001).

It is widely recognized that aerobic or facultative pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa* and β-hemolytic streptococci are the primary causes of infection of both acute and chronic wounds (Daltrey et al. 1981; Halbert et al. 1992; Sehgal and Arunkumar 1992). However, the distinction between infected and colonized wounds has to be done on a clinical

Table 2 Type of cells involved in the wound healing process

Cell type	Function in wound healing
Platelets	Involved in thrombus formation
	Rich source of inflammatory mediators including cytokines
	Major initial stimulus for inflammation
Neutrophils	First cells to infiltrate the wound
	Phagocytosis and intracellular killing of invading bacteria
Monocytes (macrophages)	Phagocytosis and killing of invading bacteria
	Clear debris and necrotic tissue
	Rich source of inflammatory mediators including cytokines
	Stimulate fibroblasts division, collagen synthesis and angiogenesis
Lymphocytes	Not clearly defined
	May produce cytokines in certain types of wounds
Fibroblasts	Produce various components of the ECM including collagen, fibronectin, hyaluronic acid, proteoglycans
	Synthesized granulation tissue
	Help reorganize the temporary ECM

perspective instead of microbiological analysis due to the universal colonization of chronic wounds. This frequently presents a wrong diagnosis that leads to the unnecessary use of antibiotics.

Wound dressings

The wound requires a protective barrier to promote the healing. Early humankind employed many different materials from the natural surroundings to treat the wounds. These include natural fibers such as wool and linen, honey, eggs and animal fat (Inngjerdingen et al. 2004; Mensah et al. 2006). Continuous development results in the development of wound dressings with improved performance. Wound dressings can be classified covering different aspects (Sai and Babu 2000; Thomas 2004) as follows:

1. Passive dressings such as gauze and tulle that act to cover the wound. Gauze can stick to the wound and disrupt the wound bed when removed, thus are suitable for minor wounds. Tulle is as greasy gauze suitable for minimal to moderate exudates.
2. Interactive dressings contain polymeric films, foams and hydrogels which are transparent and permeable to water and atmospheric oxygen. These are suitable for heavily exudating wounds (foams and hydrogels) and good barriers against permeation of bacteria to the wound environment.
3. Bioactive dressings such as hydrocolloids, alginates, collagen and hydrofibers produced from a variety of biopolymers such as collagen, hyaluronic acid, chitosan, alginate and elastin (Falabella 2006; Queen et al. 2004). These types of dressings have the ability to modify facing the physiological condition of the wound, promoting the healing. The bioactive dressings normally contain active ingredients such as antimicrobials and antibiotics (Queen et al. 2004) or can target the reduction of high protease levels on the wound (Cullen et al. 2002; Vachon and Yager 2006). Depending on the wound type and its healing, one or more different types of dressings can be applied. Table 3 describes the desirable properties of wound dressings and their impact on the healing process.

Considering the above characteristics, biomaterials have soon been used as wound dressing materials. They are designed to have an impact in the local wound environment beyond moisture management. Herein, the characteristics of protein-based materials and their action on the wound healing will be described.

Commercial protein-based wound dressings

Collagen

The development of collagen wound dressings is a consequence of its structural and functional significance in wound healing process. Collagen is the most abundant protein of extracellular matrix (ECM) providing support to connective tissues such as skin, tendons, bones, cartilage, blood vessels and ligaments (Eyre 1980; Lee et al. 2001a; Wong Po Foo and Kaplan 2002). It constitutes 30% of all protein found in the body acting as a natural scaffold for cell attachment, migration, proliferation, differentiation and survival (Yang et al. 2004). Collagen possesses high mechanical strength, good biocompatibility, low antigenicity, biodegradability, and the ability to promote cellular attachment and growth, which makes this a valuable protein for

Table 3 Properties of wound dressings and their impact on healing

Properties	Impact on wound healing
Debridement (wound cleansing)	Enhances migration of leukocytes into the wound bed
	Supports accumulation of enzymes
Provide and maintain moist	Prevents desiccation and cell death
	Promotes epidermal migration, angiogenesis and connective tissue synthesis
	Supports autolysis by rehydration of desiccated tissue
Absorption (blood and excess of exudate)	Excessive exudate blocks the proliferation and cellular activity and degrades connective tissue, factors that delay the healing
	Causes maceration of healthy tissue surrounding the wound
Permeable (water, vapor, air)	Permeability to water vapor controls the management of exudate
	Low tissue oxygen levels stimulate angiogenesis
	High tissue of oxygen stimulates ephitelialization and fibroblasts
Bacterial barrier	Infection prolongs the inflammatory phase and delays collagen synthesis, inhibits epidermal migration and induces additional tissue damage
Provide thermal insulation	Normal tissue temperature improves the blood flow to the wound bed and enhances epidermal migration
Low adherence	Adherent dressings may be painful and difficult to remove causing further tissue damage

biomedical applications (Lee et al. 2001a). Furthermore, the abundance of functional groups along the collagen polypeptide backbone allows the incorporation of genes, growth factors and other biological molecules (Harley and Gibson 2008).

Collagen sutures and extrude fibers were used to cover the exposed areas of wounded skin during the Second World War. Since then, collagen has been extensively applied for the development of wound dressings. Collagen films are made by casting collagen solutions onto methacrylate surfaces, which are thin and difficult to handle; thus, cross-linking is necessary. UV irradiation increased the mechanical strength of the films, and when implanted in animals, a very mild inflammatory response was observed along with fibroblast attachment to the collagen surface (Dunn et al. 1967). Blends of collagen films with nylon and silicon increased the mechanical strength and have been shown to be potential wound dressings exhibiting rapid epithelialization with little inflammatory response (Shettigar et al. 1982; Smith 1995). The incorporation of antimicrobial agents (Man et al. 2007) and antioxidants (Gopinath et al. 2004) on collagen films was released in a controlled manner, promoting the wound healing.

Collagen sponges are normally produced by lyophilization of collagen gel dispersions or acidic solutions (Zhong et al. 2010). These are suitable platforms for wound dressings because the large pores and interconnectivity enhances in vitro cellular attachment and growth and promote wound tissue infiltration in vivo (Doillon 1987). As advantages, collagen sponges often have poor biostability and low mechanical strength, and wound contraction easily occurs (Auger et al. 1998; Berry et al. 1998; Ono et al. 1999). Extensive modifications by cross-linking (Garcia et al. 2008; Powell and Boyce 2007) or blending with other natural and synthetic polymers such as ECM components (Ding et al. 2008; Doillon et al. 1987; Ruszczak 2003), chitosan (Man et al. 2007; Wang et al. 2008a), polycaprolactone (Dai et al. 2004; McClure et al. 2011), polylactide–polyglycolide (PLGA; Chen et al. 2004, 2006a) and polyurethane (Wu et al. 2003) improved the mechanical properties due to the formation of intra- and intermolecular covalent bonds. Moreover, these collagen-based sponges inhibited the collagen matrix from contracting, accelerating the healing. The incorporation of ECM components such as fibronectin, elastin and glycosaminoglycans (GAGs) are important in guiding the cell physiology and behavior in wound healing (Ding et al. 2008; Doillon et al. 1987; O'Brien et al. 2004; Ruszczak 2003). Addition of growth factors (Ono et al. 1998; Wang et al. 2008a) onto collagen sponges prevents wound contraction by promoting faster wound closure. Recently, the same behavior was observed by the incorporation of a herbal formulation into a collagen sponge, with improved tissue regeneration and collagen content at the wound site (Kumar et al. 2010). The ECM is composed of collagen nanoscale fibers which provide structural integrity and mechanical strength to the skin. Electrospun collagen was found to be the most biomimetic nanofibrous scaffolds similar to the native ECM. Electrospun collagen matrices exhibited excellent biocompatibility and accelerated wound healing, along with inhibition of wound contraction in the early stage of wound healing (Powell et al. 2008; Rho et al. 2006). Moreover, electrospun collagen blends with chitosan

(Chen et al. 2008) and PLGA (Liu et al. 2010) also showed accelerated wound healing when compared to collagen sponges. There are several commercially available collagen-based wound dressings. Table 4 describes their composition and function observed during wound healing.

Gelatin

Gelatin is a natural polymer that is derived from collagen and is commonly used for pharmaceutical and medical applications because of its biodegradability (Balakrishnan and Jayakrishnan 2005; Ikada and Tabata 1998; Kawai et al. 2000; Yamamoto et al. 2001) and biocompatibility in physiological environments (Kuijpers et al. 2000; Yao et al. 2004). Due to its easy processability and gelation properties, gelatin has been manufactured in a range of shapes including sponges, injectable hydrogels and gelatin microspheres which normally are incorporated in a second scaffold such as a hydrogel.

Gelatin has been applied as a dressing showing improved wound healing. Cationized gelatin hydrogel incorporating growth factors was applied to the round corneal defects in rabbits (Hori et al. 2007). This resulted in a reduction in the epithelial defect in rabbit corneas accompanied by a significantly enhanced epithelial proliferation with accelerated ocular surface wound healing. In a similar study, gelatin sponges incorporating growth factor were used to treat pressure-induced decubitus ulcers (Jiang et al. 2008; Kawai et al. 2005). It was shown that the release of growth factors promotes accelerated wound healing and induces neovascularisation. A bilayer wound dressing prepared from gelatin sponges and elastomeric polyurethane membranes were used for the incorporation of epidermal growth factor (EGF; Huang et al. 2006; Ulubayram et al. 2001). The prepared systems were tested in vivo experiments on full-thickness skin defects created on rabbits with no foreign body reaction.

The release of antimicrobials agents such as catechol (Adhirajan et al. 2009), cyclic adenosine monophosphate which is a second messenger and regulator of human keratinocyte proliferation (Balakrishnan et al. 2006) had been shown to avoid wound infection and promoted accelerated healing and re-epithelialization of full-thickness wounds. Gelatin blends with alginate (Balakrishnan et al. 2005) applied to full-thickness wounds showed the formation of new skin; chitosan (Deng et al. 2007) has been shown to have antimicrobial properties with improved mechanical properties (Yang et al. 2011). A bilayer gelatin/chondrointin-6-sulfate/hyaluronic acid dressing grafted to the dorsum of mice has positive effect on promoting wound healing, but also has a high rate of graft take (Wang et al. 2006). Electrospun gelatin and poly(L-lactide) (Gu et al. 2009) and gelatin/fibrinogen (Dainiak et al. 2011) showed controlled evaporative water loss and promoted fluid drainage ability and excellent biocompatibility, therefore having potential application as wound dressing.

Fibrin

Fibrin is a protein matrix produced from fibrinogen, which can be autologously harvested from the patient (Aper et al. 2007), providing an immunocompatible carrier for the delivery of active biomolecules, especially cells. Polymerized fibrin is a major component of blood clots and plays a vital

Table 4 Commercial collagen-based wound dressings

Dressing	Composition	Application
Alloderm™	Acellular dermis from cadaveric skin origin	Autograft in the resurfacing of burn wounds reconstruction due to its human origin (Kearney 2001)
Integra™	Bovine tendon collagen and shark GAGs	Split-thickness skin grafts; treatment of leg ulcers and wound closure of severe burn wounds (Fitton et al. 2001)
Promogram®	Animal collagen (55%) with oxidized regenerated cellulose (45%)	Absorb excess proteases from the wound surface (Schönfelder et al. 2005)
Puraply®	Reconstructed type I porcine collagen	Partial- and full-thickness wounds including chronic wounds, donor sites and for MOHS surgery (Sanjay et al. 2009)
Fibrocol Plus®	Animal collagen 90% with an alginate 10%	Partial thickness wounds, venous ulcers, acute traumatic wounds, second degree burns
Apligraft™/Graftskin™	Human fibroblasts and bovine tendon collagen gel	Venous leg ulcers and diabetic foot ulcers (Curran and Plosker 2002)
Orcel™	Human epidermal keratinocytes and dermal fibroblasts) cultured in a type I bovine collagen sponge	Acute surgical excisions (Still et al. 2003)

role in the subsequent wound healing response (Neidert et al. 2002). Fibrin naturally contains sites for cell binding and therefore has been investigated as a substrate for cell adhesion, spreading, migration and proliferation (Ehrbar et al. 2005). Fibrin glue is a biological adhesive also used in surgery (abdominal, thoracic, vascular, oral, endoscopic) due to its haemostatic, chemotactic and mitogenic properties (Le Nihouannen et al. 2006). Fibrin glue mimics the last step of the in vivo coagulation cascade through the activation of fibrinogen by thrombin, resulting in a clot of fibrin with adhesive properties (Oju et al. 2005). Fibrinogen is converted into a monomeric form of fibrin by thrombin, forming a clot. The concentration of fibrinogen is 20–40 times higher in fibrin sealant products than in body fluid. Fibrin provides a material that can be rapidly invaded, remodeled and replaced by cell associated proteolytic activity (Schmoekel et al. 2004). Moreover, due to its biomimetic and physical properties, it is also widely used as a cell carrier to many cell types, such as keratinocytes, urothelium cells, tracheal epithelial cells (Wechselberger et al. 2002), murine embryonic stem cells (Willerth et al. 2006) and mesenchymal progenitor cells (Schantz et al. 2005).

Fibrin is applied as a wound dressing specially because of its sealant properties showing to be effective as an adhesive bandage for treating major renal stab wounds (Griffith et al. 2004; Morey et al. 2001); also, the use of fibrin glue on wound healing in the oral cavity has a positive effect when compared with traditional suture techniques (Baughman et al. 2003; Yücel et al. 2003). The biomechanical strength of skin incision wounds was increased when treated with a fibrin sealant (Jørgensen et al. 1987). Moreover, in vivo wound healing requires fibroblast growth and collagen synthesis, which is stimulated in the presence of fibrin (Michel and Harmand 1990). Wound contraction was also found to be inhibited by the presence of fibrin (Farahani 2007). Fibrin scaffold was used in order to enhance the delivery of adenovirus encoding endothelial nitric oxide synthase (eNOS; Breen et al. 2008). It was shown that fibrin delivery of adenovirus enhanced eNOS expression, inflammatory response and a faster rate of re-epithelialisation. Full-thickness wounds treated with fibrin scaffolds seeded with keratinocytes were shown to promote wound closure (Bannasch et al. 2008) and promote the delivery of epithelial cells that assist wound healing (Grant et al. 2002). Autologuous fibrin sealants produced with commercially available devices (CryoSeal® and Vivostat®) and those industrially produced homologous fibrin sealant Tissucol/Tisseel® were compared in their ability for the formation and stability of clots in an in vitro model mimicking in vivo conditions (diffusion of protease inhibitors and proteolytic digestion; Buchta et al. 2005). It was shown that clot liquefaction occurs faster for all autologous fibrin sealants clots. A novel chimeric protein produced by the fusion of the fibrin-binding domain with epidermal growth factor demonstrated its potential for repairing injured tissues (Kitajima et al. 2009).

Innovative protein-based wound dressings

Silk fibroin

Silks are naturally occurring protein polymers produced by a wide variety of insects and spiders (Kaplan et al. 1994, 1998; Vollrath and Knight 2001). The diverse functions of silks range from web construction and prey capture (spider webs), safety lines (draglines) to reproduction (cocoons; Altman et al. 2003; Winkler and Kaplan 2000; Wong Po Foo and Kaplan 2002). Silk in its natural form is composed of a filament core protein, silk fibroin, and a glue-like coating consisting of sericin proteins. The most widely studied silks are cocoon silk from the silkworm *Bombyx mori* and dragline silk from the spider *Nephila clavipes* (Jin and Kaplan 2003; Vollrath and Knight 2001). Silk fibers from the domesticated silkworm *B. mori* consist of two proteins—a light chain (≈26 kDa) and a heavy chain (≈390 kDa)—which are present in a 1:1 ratio and are linked by a single disulfide bond that holds the fibroin together (Zhou et al. 2000). These proteins are coated with a family of hydrophilic proteins, sericin (20–310 kDa), which accounts for 25% of the silk cocoon's mass (Inoue et al. 2000; Kaplan et al. 1998; Zhou et al. 2000). The amino acid composition of silk fibroin from *B. mori* consists mainly of glycine (Gly, 44%), alanine (Ala, 29%) and serine (Ser, 11%; Vasconcelos et al. 2008). The crystalline domains in the fibers consist of Gly-X repeats, with X being Ala, Ser, threonine and valine (Val; Zhou et al. 2001). In the solid state, silk fibroin can assume two polymorphs: The silk I structure is water-soluble, and upon exposure to heat, physical spinning and organic solvents easily converts to silk II structure (Jin and Kaplan 2003; Kaplan et al. 1998; Zhou et al. 2001). The β-sheet structures (silk II) are asymmetrical, with one side occupied by hydrogen side chains from glycine and the other occupied by the methyl side chains from the alanine that populates the hydrophobic domains. Silk II is water-insoluble as well in several solvents, including mild acid and alkaline conditions and several chaotropes.

Silk fibers from *B. mori* have been primarily used in biomedical applications as sutures (Zhang 2002) and, during decades of use, silk fibers proven to be effective in many clinical applications. Nevertheless, immunological reactions observed to virgin silk suture have been attributed to the sericin protein (Moy et al. 1991). It has been shown that sericin is a potential allergen causing a type I allergic reaction (Panilaitis et al. 2003; Rossitch et al. 1987). In this

way, removal of sericin from silk is necessary to prepare non-allergic and non-cytotoxic silk-based materials. However, a recent study using sericin/gelatin blends for the fabrication of films and sponges reported cytocompatibility using feline fibroblast cells and low immunogenicity (Mandal et al. 2009b).

Silk fibroin-based biomaterials can be obtained with different morphologies: Silk films can be prepared by solvent casting or layer-by-layer deposition of solutions (Hofmann et al. 2006; Huemmerich et al. 2006); SF sponges or scaffolds can be formed after lyophilization, porogens or gas foaming (Wang et al. 2008b); SF hydrogels are formed via sol–gel transitions, sonication, vortexing or the presence of acid and/or ions (Mandal et al. 2009a); SF nanofibers are prepared by electrospinning (Unger et al. 2004); and SF micro/nanospheres have been prepared by water/oil emulsion, spray drying, lipid vesicles, salt leaching and sonication (Hino et al. 2003; Wang et al. 2007). To be further used, it is necessary to induce β-sheet crystallization so that silk-based materials become water-insoluble and more slowly degraded. This can be achieved through the use of organic solvents such as methanol and formic acid, mechanical stress, high concentrations of salts and thermal treatment (Drummy et al. 2005; Um et al. 2001). Water-based annealing procedure and very slow drying have been shown to induce the formation of the β-sheet crystal of SF materials (Jin et al. 2005; Lu et al. 2011). According to the US Pharmacopeia, a degradable material is defined as one that "loses most of its tensile strength within 60 days" post-implantation in vivo. By this definition, silk is classified as non-degradable. However, based on the literature, fibroin is proteolytically degradable over longer time periods (Horan et al. 2005). Pure SF and blend systems had been applied in the development of new wound dressing materials, and they have been extensively studied using animal models. Table 5 describes some of the applications of silk fibroin as a wound dressing.

Overall, the healing properties presented by the SF-based materials are related to the physical properties of SF such as water absorption and vapor permeability. The ability to absorb wound exudate forms a flexible dressings that sticks to the wound, preventing excessive flow cell-proliferating substances, exudate and proteins. At the same time, smooth regeneration of the skin is accelerated because the flexible dressings moves when the skin moves, without stimulating the wound

Keratin

Keratin is the major structural fibrous protein providing outer covering such as hair, wool, feathers, nails and horns of mammals, reptiles and birds (Feughelmann 1985). Keratin fibers, such as wool and human hair, consist of two major morphological parts: the cuticle layer which is composed of overlapping cells that surround the cortex and the inner part of the fiber. Keratin proteins can be roughly classified into two groups: the intermediate filament proteins (IFPs) and the matrix proteins. The most abundant are the IFPs, also known as α-keratin, that reside in the fiber cortex. They have an α-helical secondary structure, are low in sulfur content and have an average molecular mass in the range of 40–60 kDa. The matrix proteins or γ-keratin are globular, have low molecular weights and are noted for the high content in either cysteine, glycine or tyrosine residues. The ones with high sulfur content can be divided into high sulfur proteins or ultra-high sulfur proteins depending on their cysteine content and have a molecular weight in the range of 11–26 kDa. The high glycine–tyrosine proteins have a molecular weight between 6 and 9 kDa. The matrix proteins function to surround the IFPs and interact with them through intermolecular disulfide bonds (Plowman 2003). The formation of the cross-linked IF–matrix composite is crucial in conferring to α-keratins their high mechanical strength, inertness and rigidity (Parry and Steinert 1992). There is also another group of keratin proteins, the β-keratin. These form the majority of the cuticle, and their function is to protect keratin fibers from physical and chemical damage. β-keratin is difficult to extract and do not form especially useful reconstituted structures (Crewther et al. 1965).

Keratins are extracted from the fibers through the use of chemicals to break the disulfide bonds. The IF and matrix proteins are converted into their non-cross-linked forms by oxidation (Breinl and Baudisch 1907; Buchanan 1977; Crewther et al. 1965; Earland and Knight 1956) or reduction (Crewther et al. 1965; Goddard and Michaelis 1934; Maclaren 1962; O'Donnell and Thompson 1964), during which cysteine is converted to either cysteic acid or cysteine, respectively. Oxidative extraction yields keratins that are hygroscopic, non-disulfide cross-linkable, water-soluble and susceptible to hydrolytic degradation at extremes pH values due to polarization of the backbone caused by the electron-withdrawing properties of the cysteic acid. These characteristics lead to biomaterials that can degrade relatively fast in vivo, i.e. in the order of days to weeks. Reduced keratins are less polar and, as a consequence, less soluble in water, more stable at extreme pH and can be re-cross-linked through oxidative coupling of cysteine groups. This results in biomaterials that persist in vivo for weeks to months. The interest of using keratin as a biomaterial in medical applications is based on several key properties that contribute to the overall physical, chemical and biological behaviors of these biomaterials. Extracted keratin proteins have an intrinsic ability to self-assemble and polymerize into fibrous and porous films gels and scaffolds. Furthermore, the presence of cell adhesion

Table 5 Application of SF as wound dressings

Dressing	Wound	Result
PVA/Chitosan/SF (PCS) sponges	Excision rat wound	Absorption of wound exudate with accelerated wound healing (Yeo et al. 2000)
SF films	Full-thickness mice skin wound	Reduced wound size by 10, faster healing about 7 days shorter when compared to control dressing (DuoActive); higher collagen regeneration and reduce inflammation (Bidwell et al. 2007)
SF/alginate sponges	Full-thickness mice skin wound	Reduced healing time in comparison to control or pure SF and alginate; significant increase of re-ephitelialization and in the number of proliferative cells (Negri et al. 1993)
Polarized hydroxyapatite (pHA) and SF composite gel	Full-thickness porcine skin wound	Higher promotive effects, re-ephitelialization and matrix formation (Okabayashi et al. 2009)
SF/sericin powder combined with amorphous SF film	NA	Inhibition of edematization (Tsubouchi 2001)
SF fiber dressing	NA	Selective sequestration of targeted proteases from wound exudate (Mcdevitt 2002)
Electrospun silk mats	NA	Loading of electrospun silk mats with EGF promoted a faster wound closure up to 90% (Schneider et al. 2009)
SF/chitosan scaffold	Murine soft tissue wound	Incorporation of human adipose-derived stem cells (ASCs) onto scaffolds enhanced wound healing and show differentiation into fibrovascular, endothelial and epithelial components of restored tissue (Altman et al. 2003)
SF/keratin films	NA	Incorporation a small inhibitor peptide showed to reduce elastase activity through the controlled release of inhibitor from the films (Vasconcelos et al. 2008)

sequences, arginine–glycine–aspartic acid and leucine–aspartic acid–valine on the keratin protein derived from wool and hair, makes keratin biomaterials able to support cell attachment and growth (Tachibana et al. 2002; Verma et al. 2008). These are the same sequences found in several ECM proteins (Hamasaki et al. 2008; Humphries et al. 1987). In the field of wound healing, several patents have been published using keratin materials as wound-healing promoters (Blanchard et al. 2001, 2000; Cowsar 2003; Van Dyke 2008; Van Dyke et al. 2001a; b). Keratin powder used as an absorbent wound dressing showed the promotion of skin healing due to the release of keratin derivative peptides to the wound (Van Dyke et al. 2001b). Cross-linked keratin powder, films and hydrogels showed significant proliferation of wound healing cell lines like microvascular endothelial cells, keratinocytes and fibroblasts. Moreover, incubation of keratin materials with lymphocytes (T cells) and activated lymphocytes showed, respectively, no proliferation and normal growth, indicating that keratin materials are non-immunogenic and that the body's normal cell-mediated immune response is not inhibited by keratin materials. These were also applied to wounds on animals (rats) and humans, and a faster healing of the wounds treated with keratin materials was observed and, in the human model, with reduced pain (Blanchard et al. 2001, 2000). Water-soluble keratin peptides derived from an oxidative extraction from human hair were shown to be wound-healing agents enhancing the proliferation of human dermal fibroblasts (Van Dyke et al. 2001a). More recently, keratin derivatives obtained either by oxidative and reductive methods were applied to burn wounds using animal and human models. The burn wounds treated with keratin materials showed a decrease in wound size and accelerated wound healing. When applied to bleeding wounds, the keratin materials formed a physical seal of the wound site, providing a porous scaffold for cell infiltration and granulation tissue formation compared to clotted blood (Van Dyke 2008). Keratin was also effectively blended with other components to form new wound dressings. Keratin–collagen sponges were used in rats showing tissue compatibility and accelerated wound healing by stimulating cell proliferation and vascularization (Chen et al. 2006b). An analogue keratin–collagen sponge containing poly 2-hydroxyethylmethacrylate was applied to burn wounds in rats. The composite showed healing promotion by allowing in vivo construction of tissue engineered epidermis (Chen et al. 2007). In another recent study, keratin–gelatin used in full-thickness wounds in dogs

promoted the healing due to the early presence of hair follicles, sebaceous gland and normal thickness of the epidermis (Thilagar et al. 2009).

Elastin

Elastin is an ECM protein known for providing elasticity to tissues and organs. As a result, elastin is most abundant in organs that need to stretch and recoil, like blood vessels, elastic ligaments, lungs and skin (Faury 2001; Martyn and Greenwald 2001; Pasquali-Ronchetti and Baccarani-Contri 1997). Elastin is synthesized by a variety of cells, including smooth muscle cells, endothelial cells, fibroblasts and chondrocytes. Elastin is an amorphous protein with about 75% of hydrophobic amino acid residues (Gly, Ala, Val) and is highly insoluble due to interchain cross-links (Ayad et al. 1994). Elastin is secreted as the precursor tropoelastin (≈72 kDa) that is soluble, non-glycosylated and highly hydrophobic (Long and Tranquillo 2003; Madsen et al. 1983; Mecham et al. 1983), which will be further converted into the insoluble elastin polymer. The tropoelastin molecule consists of two types of domains encoded by separate exons: hydrophobic domains with many Gly, Val, Ala and Pro residues which often occur in repeats of several amino acids, like Gly-Val-Gly-Val-Pro, Gly-Val-Pro-Gly-Val and Gly-Val-Gly-Val-Ala Pro, and hydrophilic domains with many Lys and Ala residues that correspond to the potential cross-linking domains of tropoelastin. The two predominant cross-links of native elastin are desmosine and isodesmosine, each involving four Lys residues that are cross-linked by lysyl oxidase. The assembly of tropoelastin into a polymeric matrix is accompanied by the elastin-binding protein (67 kDa) that releases tropoelastin into a pre-formed microfibrillar network, which serves as a scaffold for tropoelastin deposition (Hinek and Rabinovitch 1994; Hinek et al. 1988; Rosenbloom et al. 1993; Ross and Bornstein 1969). The lysine residues become further modified by lysyl oxidase, allowing cross-linking into a stable polymeric matrix.

Elastin can be used in biomaterials in different forms including insoluble elastin, occurring in autografts, allografts and xenografts, decellularized extracellular matrix and in purified elastin preparations. By synthetic or recombinant techniques, repeated elastin-like sequences had also been used in biomaterials. Soluble elastin is obtained from the hydrolysis of insoluble elastin with oxalic acid or potassium hydroxide (Jacob and Robert 1989; Partridge et al. 1955). These treatments will not release tropoelastin from insoluble

Table 6 Application of elastin-based wound dressings to different types of wounds

Dressing	Wound	Result
Collagen scaffolds coated with elastin	Full-thickness skin wound	Improved dermal regeneration and reduce wound contraction (De Vries et al. 1995)
Collagen scaffolds coated with elastin	Porcine excision wound	Reduced wound contraction, improved tissue regeneration and absence of myofibroblasts when compared to control (Lamme et al. 1996)
Collagen/elastin dermal substitute	Porcine excision wound	Fibroblasts proliferation and reduced migration of unwanted subcutaneous fibroblasts into the wound; reduced degradation of the implanted dermal substitute (Lamme et al. 1998)
Collagen/elastin membranes	Rat excision wound	Serves as a template for the formation of neo-dermis (Hafemann et al. 1999)
Collagen/elastin dermal substitute	Clinical trial	Skin elasticity was improved (Cullen et al. 2002; Hinek et al. 2005) and other parameters like rete ridges, basement membrane maturation and epidermal thickness were also improved (van Zuijlen et al. 2002).
Alginate/hybrid elastin-derived peptides	Rabbit ear skin defect wound model	Promotion of attachment of human dermal fibroblasts; significantly greater ephitelialization and a larger volume of regenerated tissue (Hashimoto et al. 2004)
Elastin proteolytic digested	Skin of nude mice	Enhanced elastic fiber deposition and synthesis (Hinek et al. 2005).
Matriderm® collagen/elastin commercial dressing	Hand burns and joint-associated defects	Dermal substitute for the treatment of severe hand burns (Haslik et al. 2007) and for the reconstruction of joint-associated defects (Haslik et al. 2010). Full range of motion was achieved in both cases with no blisters and scars.

elastin, but will break peptide bonds, yielding soluble fragments of elastin and leaving the cross-links intact (Jacob and Robert 1989; Partridge et al. 1955). It has been shown that elastin-soluble peptides influence signaling, chemotaxis, proliferation and protease release via the elastin receptor (Duca et al. 2004). Therefore, biomaterials containing solubilized elastin may exert biological effects like increasing elastin synthesis. The self-assembly behavior of elastin was used to obtain different biomaterials like hydrogels (Mithieux et al. 2004; Wright et al. 2002), films (Daamen et al. 2007), nanoparticles (Herrero-Vanrell et al. 2005), sponges (Bellingham et al. 2003) and nanoporous materials (Reguera et al. 2004). These forms can be further applied in cellular orientation, small-diameter blood vessels and drug or growth factor delivery systems. Elastin-like polymers and hybrids of the same with other proteins have been extensively studied. These offer the possibility to produce an assortment of biomaterials with specific functions like manipulation of the transition temperature (Urry 1997) and high-molecular-mass polymers (Lee et al. 2001b, c; Wood et al. 1986). Elastin-based materials have been applied as skin substitutes to treat burn or chronic wounds. Table 6 presents some examples of elastin-based dressings applied to different types of wound models.

As a final remark, the use of collagen and elastin for the development of biomaterials and wound dressings leads to minor failures because these proteins will mimic their function as ECM. On the other hand, using fibrous proteins such as silk fibroin and keratin, due to their place in nature, one would not expect that they could be such valuable materials. Silk fibroin and keratin are characterized by highly repetitive amino acid sequences that result in the formation of relatively homogeneous secondary structures via self-assembly. The ability of these proteins to self-assemble into various physical states was exploited for the development of new biomaterials. These have been shown to undergo materials with improved mechanical strength, control of morphology and surface modifications options, allowing their application in controlled delivery systems and tissue engineering. This review showed that wounds treated with these materials have been shown to promote the healing by enhanced cellular proliferation, growth and differentiation, and reduced inflammation when applied to in vivo models. Despite the advantages shown by collagen-based dressings and the availability in the market, there are still concerns related to wound contraction and scarring, as mentioned. The high cost of pure collagen, the variability in the physicochemical and degradation properties, which are dependent on the collagen source and processing (Lee et al. 2001a), lead to the use of other natural proteins for wound dressing applications. In addition, the sterilization of collagen constitutes a problem because almost all sterilization methods induce modifications to collagen (Reis et al. 1996). In this way, due to the low cost and the easy process, silk fibroin and keratin are presented as good candidates for wound dressing materials.

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