Fibrin-Based Biomaterial Applications in Tissue Engineering and Regenerative Medicine

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16.1 Background of Fibrin Biomaterials

16.1.1 Background with Biology

Fibrin is a fibrillar biopolymer that is naturally formed during blood clotting. Hemostasis is a primary role of fibrin, but fibrin also functions as a provisional matrix during wound healing. Fibrin possess the properties suitable for its use in regenerative medicine; fibrin is capable of conveying matrix proteins such as fibronectin and growth factors (Makogonenko et al. 2002; Rybarczyk et al. 2003; Mosesson 2005; Laurens et al. 2006a, b; Wolberg 2007; Janmey et al. 2009). Given these features, fibrin has been widely studied in biomedical research for its ability to repair hard and soft tissues (Hubbell 2003; Falanga et al. 2007; Ahmed et al. 2008; Breen et al. 2009a, b; Davis et al. 2011; Oh et al. 2014).

The biological functions of fibrin involve its structure. A number of variables can influence the structure of fibrin, including the local pH, ionic strength, and the concentrations of calcium and thrombin (Mosesson 2005; Wolberg 2007). The thrombin concentration present at the time of gelation has important influences on fibrin clot structure. The low thrombin concentrations produce fibrin clots that are turbid and composed of thick, loosely-woven fibrin strands. Higher concentrations of thrombin produce fibrin clots that are composed of relatively thinner, more tightly-packed fibrin strands (Collet et al. 2000; Wolberg 2007). Thrombin exposes the cryptic fibronectin-binding sites in fibrinogen and that fibronectin mostly bound to polymerized fibrin but rarely bound to fibrinogen (Makogonenko et al. 2002) and modulates the fibronectin-binding capacity of fibrin and that this modulation of thrombin contributes to integrin phosphorylation of the cells (Oh et al. 2012). The structure of the fibrin biomaterials affects their biological functions. Thus, it should be optimized for specific applications in tissue engineering and regenerative medicine.

16.1.2 Biodegradation of Fibrin: Fibrinolysis

The biodegradation process of fibrin material is known as the fibrinolysis or fibrinolytic system, which is mediated by plasmin (Baron and Kneissel 2013; Park et al. 2017). Briefly, fibrin degradation can be catalyzed by cell-surface-associated plasmin, which formed after binding

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I. Noh (ed.), *Biomimetic Medical Materials*, Advances in Experimental Medicine and Biology 1064,
https://doi.org/10.1007/978-981-13-0445-3_16

soluble plasminogen and plasminogen activators (tissue-type plasminogen activator; t-pA and urokinase-type plasminogen activator; u-pA). In particular, the lysine-binding domains of plasminogen play an important role in the binding of plasminogen to fibrin for the fibrin degradation. In the inhibition of the fibrinolytic system, the plasminogen activator inhibitor-1 (PAI-1) or α2-antiplasmin (α2Ap) neutralize the plasminogen activators and block the interactions between binding domain of plasminogen and fibrin structures. Therefore, the biochemical interactions with plasminogen, fibrin, and plasminogen activators are contributed for controls of fibrin degradation process (Baron and Kneissel 2013; Park et al. 2017).

16.2 Tissue Engineering Applications Using Fibrin Biomaterials

At present, various pre-clinical/clinical approaches have been actively developed for regeneration of damaged tissues and wound healings using fibrin-based biomaterials (Table 16.1). In particular, fibrin can be dimensionally modified (two−/three-dimensional scaffolds) or its phasic characteristics (injectable or implantable matrices) can be fabricated to promote biological interactions in optimal tissue regeneration for wound healing and functioning restorations. According to target tissue defects or physiological environments, several therapeutic techniques have been implemented to improve mechanical, physical, chemical, or biological properties (Lee and Kurisawa 2013; Li et al. 2015).

16.2.1 Skin Tissue Engineering

Skin is the largest organ in the human body and consists of approximately 10% of the whole body weight. It is a crucial barrier between the internal and external with three distinct layers: the epidermis, the dermis, and the hypodermis (or subcutaneous tissue) (Chaudhari et al. 2016; Huang and Fu 2010; MacNeil 2008). The epidermis is the outermost layer to form a highly effective barrier against infectious pathogens from the external environments and maintain appropriate or optimal hydration (Huang and Fu 2010). Although capillary structures are formed under epidermis layer, 95% keratinocyte cells were contained in the epidermis without the vasculature networks. The dermis layer is between the epidermis and the hypodermis with connective tissues which are composed of fibroblasts, macrophages, and adipocytes (Priya et al. 2008). It has the primarily role to generate appropriate stress-strain mechanical responses by matrix components like collagen, elastin, and extrafibrillar matrix (MacNeil 2008). The hypodermis is the lowermost layer and below the dermis of vertebrate skin and has similar cell types to the dermis; fibroblasts, adipose cells, and macrophages. Compared to the dermis, the hypodermis mainly consists of loose connective tissue and subcutaneous fat with large blood vessels and nerves which cannot be found in epidermis and dermis tissues. Therefore, healthy skin tissue has various cell types such as keratinocytes, fibroblasts, or mesenchymal stem cells to regenerate complex tissue constructs and restore their functions (MacNeil 2008).

Fibrin has been utilized to induce skin tissue regeneration as vehicles for bioactive molecules to promote wound healing, delivery carriers for multiple cells like keratinocytes, fibroblast-like cells, and mesenchymal stem cells, or sealants for skin graft fixation to stop the bleeding (Bensaid et al. 2003; Jimenez and Jimenez 2004; Wechselberger et al. 2002).

16.2.2 Cardiac/Vascular Tissue Engineering

The cardiovascular system is the hemodynamic tissue complex with complicated responsiveness. The major components of the system are heart valves, cardiac muscles and the blood vasculatures, which are significantly challenging to regenerate or heal within the limited golden time. The cardiovascular tissues should have

Table 16.1 Tissue engineering applications using fibrin biomaterials

Target tissues	Summary	References
Skin tissue engineering	Rapid wound closure and improvement for elastic tissue regeneration	Huang and Fu (2010), Laurens et al. (2006a, b), Priya et al. (2008)
Cardiac/vascular tissue engineering	Injectable fibrin matrices to decrease infarct size, increase blood flow to ischemic myocardium, and improve cardiac function	Black et al. (2009), Chang and Niklason (2017), Cummings et al. (2004), Flanagan et al. (2007), Grassl et al. (2003), Huang et al. (2007), Ye et al. (2000)
Musculoskeletal tissue engineering	Biomimetic micro-architectures of the natural nanostructured features of bone and cartilage using the fibrin matrices having osteogenic or chondrogenic factors	Ben-Ari et al. (2009), Connelly et al. (2004), Eyrich et al. (2007), Koob et al. (2011), Lee et al. (2012), Neovius and Kratz (2003), Noori et al. (2017), Park et al. (2017), Passaretti et al. (2001), Peretti et al. (2006), Perka et al. (2000), Schek et al. (2004), Westreich et al. (2004)
Nervous tissue engineering	Central and peripheral nervous system regenerations using various concentrated fibrin matrices or chemically-modified fibrin.	Chernousov and Carey (2003), Herbert et al. (1998), Johnson et al. (2010), Sakiyama-Elbert and Hubbell (2000), Sakiyama et al. (1999), Tsai et al. (2006)

flexible responsiveness against various mechanical stimulations such as pressure, blood shear stress, molecular permeability in dynamic fluidics, and immunological responses (Gebara et al. 1997; Pober and Tellides 2012). In particular, severed ischemic cardiac tissue damages or injuries are irreversible or limitedly viable to restore vital functions (Hasan et al. 2015).

Grassl et al. developed and demonstrated the mechanically-modified fibrin-based tubular constructs as vascular grafts (Grassl et al. 2003). By controlling and balancing between fibrinolysis and cell-produced collagen matrix formation, the modified fibrin can be improved in mechanical strength like ultimate tensile strength or tensile modulus (Grassl et al. 2003). Moreover, cardiomyocytes can be encapsulated using the fibrin material and the strategy influenced cell alignments like cardiac muscle bundles for functioning restoration (Black et al. 2009). In particular, 3-D fibrin architectures could guide cardiac cell alignments and maintained synchronous beating in the *in-vitro* environment (Huang et al. 2007)

16.2.3 Musculoskeletal Tissue Engineering

The musculoskeletal complex is the major system to support organs and tissues as well as allow the appropriate movements with structural stabilities. The system has the bone skeleton and fibrous connective tissues. The mineralized tissue or bone in the system plays a critical role to protect the vital organs, provide locomotion of body, and produce blood cells. Moreover, fibrous connective tissues like ligaments, muscles, cartilage, or tendons can contribute the fundamental mobility after integration with bone (ligament, tendon, or cartilage) or muscles (tendon) (Stevens 2008).

In bone constructs, there are two major patterns to generate mechanical responses by remodeling tissues like compact (cortical bone) and trabecular patterns (cancellous bone) (Clarke 2008; Stevens 2008). In particular, the bone remodeling process can be contributed by significant cell activations of osteoblasts for regeneration and osteoclasts for destruction (Stevens 2008) However, if the physiological balance for bone remodeling is lost by diseases or greater defects than osteogenic wound healing, various osteoconductive or osteoinductive materials could be critically considered to promote bone regeneration as well as bone substitutes (Noori et al. 2017; Stevens 2008).

Fibrin matrices fundamentally have numerous proteins and growth factors so, they have widely utilized in bone tissue engineering in various preclinical and clinical scenarios. They can biologically contribute the upregulation of osteoblast expressions and significantly promote bone tissue

regeneration (Ben-Ari et al. 2009; Schek et al. 2004; Stevens 2008). Although fibrin has these great biological or biochemical properties, it is challenging to improve and modify rapid biodegradability and poor mechanical properties for skeletal structure neogenesis. Therefore, fibrin-incorporated bioactive composite materials have been developed using inorganic materials to have similar compositions to bone minerals with mechanical strength and enhance osteogenesis or organic materials to enable 3-D fabrications for favorable architectures with biodegradability and characterize biochemical/biological properties (Stevens 2008).

Of fibrous connective tissues in the musculoskeletal system, the cartilage is major structural component of ears, nose, or joint areas with higher stiffness and less flexibility than other fibrous tissues (Lee et al. 2012; Neovius and Kratz 2003; Passaretti et al. 2001; Peretti et al. 2006). In particular, articular cartilage has no vascular structures or nerves so, nutrition can be diffused to chondrocytes and the articular cartilage can particularly be too slowly remolded to have tissue regeneration or repair (Zhang et al. 2009). It is placed on the surface of joints to provide protection and movements of skeletal structures under compressive forces. Because mechanical responses of articular cartilage structures are significantly considered in frictional, compressive, or shear loading environments, cartilage can be demonstrated as resilient and viscoelastic tissue constructs at the skeletal joints (Zhang et al. 2009).

For the cartilage tissue engineering, fibrin material is widely studied and applied for various preclinical studies with clinical implications like chondrocyte-fibrin constructs or injectable fibrin gel containing cells to promote cartilage formations (Eyrich et al. 2007; Horak et al. 2014; Makris et al. 2015; Vinatier et al. 2009). However, environmental specificity of the cartilage construct under biomechanical stimulations can be a challenge for the cartilage regeneration using 3-D fibrin scaffold so, chondrocyte-associated fibrin sealant or fibrin glue have been popularly utilized.

16.2.4 Nerve Tissue Engineering

Nerve tissue categorizes two major parts like central nervous system (CNS) and peripheral nervous system (PNS) to regulate body functions. It mainly consists of nerve cells (neurons) to transmit impulses and glial cells (neuroglia) to provide nutrients and oxygen to neurons. The CNS has sophisticated dynamic networks with physicochemical communications to exchange sensed information. PNS consists of sensory and motor axons surrounded my myelin sheaths which Schwann cells produced (Johnson et al. 2010, 2013; Schmidt and Leach 2003; Subramanian et al. 2009). In various traumatic injuries or diseased destructions, CNS and PNS have different capacity of regeneration; CNS axons cannot be regenerated but peripheral nerves can be healed by extending new axonal sprouts (Schmidt and Leach 2003).

To guide the directional orientations with new nerve tissue regeneration, various biomaterials have been developed and utilized as the nerve conduits in preclinical and clinical situations (Sakiyama-Elbert and Hubbell 2000; Tsai et al. 2006). In particular, fibrin matrices have been used to fill hollow nerve conduits across the nerve defect regions to promote axonal regeneration and growth (Tsai et al. 2006). Moreover, fibrin scaffolds have been limitedly used for spinal cord regeneration or neural fiber formations at the early stage (Johnson et al. 2010).

16.3 Technical Applications for Tissue Regeneration in Fibrin Biomaterials

For the strategic applications for tissue engineering using fibrin matrices, various fabrication and modification techniques have been developed and applied for preclinical and clinical scenarios (Table 16.2). In particular, target tissues or injured defect dimensions should be significant considerations to manufacture fibrin products for the appropriate medical or surgical treatments. Commonly, fibrin gel has been widely considered

Table 16.2 Technical applications of fibrin for tissue regeneration

Target strategies	Summary	References
Injectable scaffold for tissue regeneration: Delivery system	Cell or biologic (drug) delivery systems for tissue regeneration	Breen et al. (2009a, b), Lee and Mooney (2001), Sacchi et al. (2014), Spicer and Mikos (2010), Tajdaran et al. (2015), Whelan et al. (2014), Yuan Ye et al. (2011)
Modified fibrin matrix for tissue engineering	Chemical modification of fibrin materials to improve mechanical properties and optimize predictable cell/tissue responses	Breen et al. (2009a, b), Hall et al. (2004), Hall and Hubbell (2004), Hall (2007), Lee and Mooney (2001), Park et al. (2017)
3D printing technique	3D bioprinting strategy with the fibrin gel material to manufacture customized architectures for tissue engineering and regenerative medicine	Gu et al. (2016), Lee et al. (2010), Lorber et al. (2014), Pati et al. (2015), Rimann et al. (2015), Xu et al. (2006)
Current clinical application	FDA-approved, clinical applicable products: Plasma-rich fibrin, fibrin sealant, or fibrin glue	Albala and Lawson (2006), Andree et al. (2008), Buchta et al. (2005), Janmey et al. (2009), Molly et al. (2006), Saltz et al. (1991); Santoro et al. (2007); Simonpieri et al. (2012)

as a sealant or a bioadhesive for hemostasis or wound closure (Mehdizadeh and Yang 2013) because the fibrin shows the minimal inflammation, foreign body reaction, or rapid degradation (Schmidt and Leach 2003).

As target cell or favorable biologic delivery systems, the injectable fibrin gel has been investigated as a carrier: such as cardiomyoblast delivery (Camci-Unal et al. 2014), bone marrow cells (Tajdaran et al. 2015), or bioactive factors (Bensaid et al. 2003; Breen et al. 2009a, b; Tajdaran et al. 2015). Injectable fibrin has been popularly investigated for bone tissue engineering applications because it is not seriously considered for any defect shapes or dimensions and simple invasive implant procedure. To improve the effectiveness and efficacy, it is required to mix the fibrin and biological components like bioactive molecules, cells (or stem cells), or other biomaterials (Li et al. 2015). Moreover, fibrin microbeads are recently studied to deliver a single cell into 3-D engineered micro-environments (or scaffolds) or directly into the injured defect sites for cartilage, cardiac muscle, skin or others (Spicer and Mikos 2010; Tajdaran et al. 2015; Whelan et al. 2014; Yuan Ye et al. 2011). It can be advantageous to more predictably control the quantities of cells or biologics with high efficacies. Fibrin-based micro-bead delivery systems can also encapsulate various stem cells to promote bone regeneration (Liu et al. 2017).

Although the fibrin has various advantages for tissue regeneration like great cell-material interactions, rapid biodegradability could be the limitation to induce appropriate tissue formation with sufficient time (Hubbell 2003; Mano et al. 2007). Therefore, the fibrin material has been modified with chemical agents to control degradability or enhance crosslinking for improvements of biological and mechanical properties (Park et al. 2017; Tallawi et al. 2015). In particular, various cell types can affect fibrin degradation rate because different biologics can be produced by biological interactions between cells and fibrin matrices (Brown and Barker 2014). Recently, Park et al. investigated that the cementoblast and osteoblast generated significantly different matrix metalloproteinases (MMPs) in *in-vitro* and modified fibrins for slow biodegradation critically contributed to promote cementogenesis and insert/integrate fibrous connective tissues within the mineralized tissues in *in-vivo* (Park et al. 2017).

For the 3-D scaffolds with geometric or architectural specificities, 3-D additive manufacturing or 3-D printing techniques have been currently highlighted and rapidly developed for biomedical applications (Gu et al. 2016; Lorber et al. 2014; Pati et al. 2015; Rimann et al. 2015; Xu et al. 2006). Of various polymeric materials for 3-D printing systems, the fibrin material is limitedly utilized as the bioink which is the hydrogel

material with biological components like cells or biologics for soft tissue engineering (Gu et al. 2016). Xu et al. demonstrated that the 3-D printing fabrication manufactured the fibrin constructs for neural tissue-guiding scaffolds (Xu et al. 2006) and Lee et al. presented the modified fibrin material with murine neural stem cells was used for build the 3-D architectures for nerve tissue formations (Lee et al. 2010).

16.4 Future Perspectives for Fibrin Biomaterials in Tissue Engineering and Regenerative Medicine

Fibrin has showed the high potential in functioning as an injectable materials, property-controlled materials with cell-material interactions, and 3-D printed scaffolds for tissue engineering and regenerative medicine. However, there are still numerous limitations like the poor mechanical properties for skeletal tissue regeneration, potential disease transmission by unpredictable biological affinities, or deformability of fibrin hydrogels. Many efforts have been contributed to improve the mechanical strength to extend applications with wide spectra and investigate synthetic biopolymeric material composite to characterize as biological or bioactive materials like polyglycolic acid and poly(lactic-co-glycolic acid).

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