

# Fibrin Glue as a Vehicle for Mesenchymal Stem Cell Delivery in Bone Regeneration

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## Tissue Engineered Bone Reconstruction: The Era of Regenerative Medicine

In order to create tissues and organs for replacement, understanding the processes of repair and regeneration is essential. The regeneration and repair of tissues are fundamentally different processes.<sup>1</sup> Tissue regeneration, which readily occurs in embryos, is almost absent in neonates (although some regenerative events have been reported) and is never observed in adults. Regeneration is a relatively slow process that seems to recapitulate many but not all the steps that occur in the embryo. In contrast, tissue repair is rapid and has been revolutionarily selected to minimize the animal's vulnerability, that is, to get the animal away from danger as soon as possible.<sup>2</sup> It was not until the late 1980s that tissue engineering was regarded as an independent branch of science. The term *tissue engineering* was initially defined by the attendees of the first National Science Foundation of the United States sponsored meeting in 1988 as "application of the principles and methods of engineering and life sciences toward fundamental understanding of structure–function relationship in normal and pathologic mammalian tissues and the development of biological substitutes for the repair and regeneration of tissue or organ function".<sup>3</sup> In 1993, Langer and Vacanti summarized the early development in this field and defined tissue engineering as "an interdisciplinary field that applies the principles of engineering and life sciences towards the development of biological substitutes that restore, maintain, or improve tissues or organ function".<sup>4</sup> The exercise of interdigitating these different functional talents into a coherent device has produced the working definition of tissue engineering: "Tissue engineering is an art and science by which synthetic compounds are

manipulated into anatomically and/or functionally specific architectures and, when required, may be integrated with biologically active agents and/or living cells such that resultant properties of the whole are precisely suited to support the specific cell life prescribed for recipient tissues".<sup>5</sup> Since then, numerous experiments have been performed to hammer out the optimal tissue engineering approach to achieve bone regeneration.

## Mesenchymal Stem Cells for Bone Regeneration

The middle embryonic layer, the mesoderm, gives rise to all of the body's skeletal elements. The term *mesenchyme* is derived from the Greek meaning *middle (meso) infusion* and refers to the ability of mesenchymatous cells to spread and migrate in early embryonic development between the ectodermal and endodermal layers. This characteristic migratory space-filling ability is the key element of all wound repair in adult organisms involving mesenchymal cells in the skin (dermis), bone (periosteum) or muscle (perimysium). It is generally agreed that in the mesoderm of an embryo, a mesenchymal stem cell is a pluripotent progenitor cell that divides many times and whose progeny eventually give rise to skeletal tissues such as bone, cartilage, tendon and ligament. By definition, these cells are not governed by or limited to a fixed number of mitotic divisions.<sup>6</sup> These cells have the capacity for extensive replication without differentiation, and they possess a multilineage development potential. In fact, many adult tissues contain populations of stem cells that have the capacity for renewal after trauma, disease or aging. It has been widely accepted that human bone



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marrow, apart from containing hematopoietic stem cells, also contains mesenchymal stem cells which contribute to the regeneration of different mesenchymal tissues such as bone, cartilage, muscle, ligament, tendon and adipose tissues.<sup>7</sup> Subsequently, a body of evidence has indicated that mesenchymal stem cells possess excellent potential for bone regeneration.

## Fibrin Glue as a Scaffold for Bone Regeneration

Scaffolds can provide necessary support for cells to maintain their differentiated functions and define the ultimate shapes of the new bones. Before considering the desired features of potential tissue engineering materials, it is useful to understand two concepts of bone regeneration for tissue engineering constructs, specifically osteoinduction and osteoconduction. Osteoinduction is defined as the ability to cause pluripotent cells, from a nonosseous environment, to differentiate into chondrocytes and osteoblasts, culminating in bone formation. An osteoinductive material guides repair in a location that would normally not heal if left untreated. Osteoconduction supports ingrowth of capillaries and cells from the host into a 3-dimensional structure to form bone. An osteoconductive material guides repair in a location where normal healing would normally occur even if untreated.

Taking the concepts of osteoconduction and osteoinduction into consideration, the desirable qualities of a bone tissue-engineering scaffold design have been postulated.<sup>5</sup> First of all, the scaffold must be able to promote maximal bone ingrowth through osteoinduction and/or osteoconduction, and it does not induce soft tissue growth at the bone/scaffold interface. Additionally, it should: (1) not exert any detrimental effects on surrounding tissues due to processing; (2) be sterilizable without loss of properties; (3) be absorbable with biocompatible components—preferably, it is absorbed in a predictable manner in concert with bone growth; (4) be malleable and adaptable to irregular bone defect sites; and (5) possess proper mechanical and physical properties, in particular, in the early stages after implantation. Most importantly, it should be user friendly; that is, easy to apply and available to surgeons at short notice.

One potential candidate material that may be used as scaffolding for tissue-engineered bone tissues is fibrin glue. Fibrin glue is a physiologically relevant matrix whose principal component, fibrin, has fundamental roles in the process of blood clotting and wound

healing. Fibrin glue, a composite of fibrinogen and thrombin, is a potentially suitable biological vehicle for cell transplantation because it has proven biocompatibility, biodegradability and binding capacity to cells. Fibrin-stabilizing factor XIII contained in fibrin glue favors migration of undifferentiated mesenchymal cells on the highly cross-linked structure of the glue, and it enhances the proliferation of these cells. The rate of resorption of fibrin glue can be controlled by varying the concentration of the fibrinolytic inhibitor apoptin.<sup>8</sup> This keeps the cells in place, increases cell survival, and improves the immediate mechanical properties of the implant. The fibrin extracellular matrix remains *in situ* while the cells proliferate and differentiate into new tissue, before the scaffold is completely resorbed. Most important of all, the fibrin glue promotes angiogenesis via chemotactic and mitogenic stimuli that promote cell migration, proliferation and matrix synthesis.<sup>9</sup> Our previous work has shown that fibrin glue can be used to deliver mesenchymal stem cells to facilitate bone regeneration in normal and chemotherapy-treated rats.<sup>10</sup> In this issue of the *Journal of the Chinese Medical Association*, Lee et al further demonstrated the usefulness of autologous fibrin glue to deliver mesenchymal stem cells for calvarial defect regeneration in rabbits.<sup>11</sup> Their study elegantly demonstrated that autologous fibrin glue better facilitated bone regeneration than macroporous biphasic calcium phosphate in the presence of mesenchymal stem cells. Their results justify further translational research to investigate the use of autologous fibrin glue as a scaffold to facilitate bone regeneration in non weight-bearing areas such as craniofacial bones.

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