Tissue Engineering Strategies for Fetal Myelomeningocele Repair in Animal Models

Miho Watanabe, Aimee G. Kim, Alan W. Flake

Department of Surgery, and Center for Fetal Research, Children’s Hospital of Philadelphia, Philadelphia, Pa., USA

Rationale for Prenatal Surgical Closure of Myelomeningocele

Myelomeningocele (MMC) represents the first non-lethal anomaly to be treated by open fetal surgery. The application of an invasive procedure with significant potential risk to the mother was felt to be justified due to the devastating neurological consequences of MMC, including lower extremity paralysis, neurogenic bladder and hindbrain herniation [1, 2]. The rationale for fetal treatment is based on the ‘two-hit’ hypothesis, where the first ‘hit’ is the primary failure of neurulation, and the second ‘hit’ is the injury to exposed neural elements caused by exposure to amniotic fluid and mechanical trauma within the amniotic space [3]. Most experimental and clinical evidence indicates that the majority of neural damage is caused by the second hit, leading to a compelling rationale for the prenatal treatment of MMC. A less invasive approach would allow for an application earlier in gestation, with a reduction in maternal and fetal risks and the potential for reduced neurological injury. Tissue engineering offers a realistic and appealing alternative approach for the prenatal treatment of MMC. This review discusses the rationale for tissue engineering in MMC, addresses recent experimental progress and describes potential future directions.

Key Words
Myelomeningocele · Fetal therapy · Tissue engineering · Minimally invasive techniques · Scaffolds · Stem cells · Fetal surgery

Abstract
Myelomeningocele (MMC), the most severe form of spina bifida, is a common and devastating malformation. Over two decades of experimental work in animal models have led to the development and clinical application of open fetal surgery for the repair of the MMC defect. This approach offers improved neurofunctional outcomes and is now a clinical option for the management of prenatally diagnosed MMC in selected patients. However, there are still opportunities for further improvement in the prenatal treatment of MMC. A less invasive approach would allow for an application earlier in gestation, with a reduction in maternal and fetal risks and the potential for reduced neurological injury. Tissue engineering offers a realistic and appealing alternative approach for the prenatal treatment of MMC. This review discusses the rationale for tissue engineering in MMC, addresses recent experimental progress and describes potential future directions.
randomized, controlled, multicenter trial, comparing in utero surgical repair of the MMC defect to standard postnatal repair [16]. The MOMS trial demonstrated conclusively that fetal surgery improves the 12- and 30-month outcomes of MMC patients, with a reduction in hindbrain herniation and the need for shunting and significant improvement in functional neurological outcomes, including the ability to walk without orthotics, setting a new standard for the treatment of eligible MMC fetuses. However, open fetal surgery for MMC is not a cure, with most patients demonstrating some degree of residual neurological deficit and some fetuses demonstrating no benefit over predicted neurological function [2]. Thus, it is clear that further improvements in the prenatal treatment of MMC fetuses are needed.

**Current Challenges in Prenatal Surgical Closure of MMC**

To significantly improve the current results of open fetal surgery for MMC, one must aim to reduce maternal risk and to further improve fetal neurological outcome. The reduction of maternal risk would presumably involve the application of minimally invasive techniques such as fetoscopic repair or ultrasound-guided methods. However, attempts thus far to utilize fetoscopic techniques have required multiple large trocars, prolonged operative times and uterine insufflation to improve visualization and overcome the obstacle of working under amniotic fluid. With these fetoscopic techniques, although reporting has been incomplete, there appears to be a higher rate of fetal loss, hemorrhagic complications, premature delivery, and technical failure to achieve closure [17–19]. To improve upon the results of open fetal surgery, truly minimally invasive techniques that could be performed rapidly through a single trocar or at most 2 small (≤2 mm) trocars will probably be needed [20]. These requirements are prohibitive for standard surgical techniques of tissue dissection and suturing and will require a simplified method to achieve tissue coverage. The second aim – that of further improvement of neurological outcome – will probably require one or more of the following: (1) achieving coverage earlier in gestation, (2) reducing the trauma associated with neurosurgical repair and (3) supporting neural survival and potentially neural regeneration. Currently, open fetal surgery is performed after 20 weeks’ gestation, which, in many cases, is clearly after some spinal cord damage has already occurred. Prior to 20 weeks’ gestation, conventional surgical techniques such as suturing and approximating tissue under tension are limited by the water content and gelatinous nature of fetal tissue. Nevertheless, the ideal repair would be performed soon after MMC can be detected at 15–18 weeks’ gestation. At that time, the MMC defect is very small (millimeters in size), raising the possibility of simpler, non-surgical techniques for closure. Given that experimental and clinical evidence supports the need for a fluid-impermeable tissue layer as the primary requirement for neural protection and reversal/prevention of the Arnold-Chiari malformation, tissue engineering is the obvious technology that comes to mind. In fact, at first glance it seems like a simple tissue engineering problem, i.e. the need to cover a small defect with a fluid-impermeable tissue layer to prevent further exposure to the nerve-ravaging effects of amniotic fluid and to prevent continued leakage of cerebrospinal fluid through the MMC defect. However, there are unique challenges in the application of tissue engineering-based technology, as it currently exists, to the in utero environment and to MMC specifically.

**Concepts of Tissue Engineering**

Tissue engineering has recently been established as an emerging field of medicine focusing on repair, replacement or regeneration of cells, tissues and whole organs [21]. It combines expertise from diverse scientific disciplines such as cell biology, bioengineering, material science, gene therapy, and pharmacology. The three main components of tissue engineering are cells, scaffolds and nutrients, all of which make up the tissue engineering construct [22, 23]. The cellular component of the construct may be either exogenous, endogenous or both. The use of exogenous cells may be required if endogenous cells cannot be stimulated to participate in tissue generation. Exogenous cells can be used to seed scaffolds or can be injected into the site to assist in tissue generation either by direct participation in tissue formation or by indirect paracrine mechanisms. Exogenous cells may be differentiated cells, multipotent stem cells or even pluripotent stem cells derived from adult, fetal or embryonic sources [24]. A particularly attractive source of cells for the prenatal treatment of MMC are amniotic fluid-derived cell populations that can be obtained by amniocentesis and rapidly expanded to be utilized as autologous multipotent stem cells [25]. The nutrient component of the tissue engineering construct may be provided by the endogenous...
Table 1. Experimental studies that provide coverage of the MMC defect using scaffolds

<table>
<thead>
<tr>
<th>Year</th>
<th>Animal type</th>
<th>Size of MMC at creation</th>
<th>Animals, n</th>
<th>Timing of repair</th>
<th>Surgical approach</th>
<th>Scaffold type</th>
<th>Scaffold Fixation</th>
<th>Timing of harvest</th>
<th>Gross inspection of MMC</th>
<th>Histological outcome</th>
<th>Neurofunctional outcome</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>rat</td>
<td>3.5 mm</td>
<td>12</td>
<td>ED18</td>
<td>open</td>
<td>N</td>
<td>gelatin</td>
<td>sealant</td>
<td>ED18–21</td>
<td>n.a.</td>
<td>epidermal ingrowth, neovascularization</td>
<td>n.a.</td>
</tr>
<tr>
<td>2011</td>
<td>rat</td>
<td>3.5 mm</td>
<td>58</td>
<td>ED18</td>
<td>open</td>
<td>N</td>
<td>gelatin</td>
<td>sealant</td>
<td>ED18–21</td>
<td>n.a.</td>
<td>epidermal ingrowth, cellular adhesion</td>
<td>n.a.</td>
</tr>
<tr>
<td>2005</td>
<td>sheep</td>
<td>2 × 3 cm (3)</td>
<td>3</td>
<td>GA79</td>
<td>open</td>
<td>N</td>
<td>collagen based</td>
<td>suture</td>
<td>PND7</td>
<td>closed, large defect¹</td>
<td>complete tissue coverage, less damage to the spinal cord</td>
<td>n.a.</td>
</tr>
<tr>
<td></td>
<td>sheep</td>
<td>2 × 3 cm (3)</td>
<td>4</td>
<td>GA79</td>
<td>open</td>
<td>NA</td>
<td>small intestinal submucosa</td>
<td>suture</td>
<td>PND7</td>
<td>closed, small defect¹</td>
<td>complete tissue coverage, less damage to the spinal cord</td>
<td>n.a.</td>
</tr>
<tr>
<td>2006</td>
<td>sheep</td>
<td>2 × 3 cm (3)</td>
<td>3</td>
<td>GA79</td>
<td>open</td>
<td>N</td>
<td>collagen based</td>
<td>suture</td>
<td>PND7</td>
<td>closed, large defect¹</td>
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<td>open</td>
<td>NA</td>
<td>small intestinal submucosa</td>
<td>suture</td>
<td>PND7</td>
<td>closed, small defect¹</td>
<td>complete tissue coverage, less damage to the spinal cord</td>
<td>n.a.</td>
</tr>
<tr>
<td>2008</td>
<td>sheep</td>
<td>2 × 3 cm (3)</td>
<td>5</td>
<td>GA86–93</td>
<td>open</td>
<td>N</td>
<td>collagen based</td>
<td>suture</td>
<td>PND7–8</td>
<td>closed, small defect¹</td>
<td>complete tissue coverage</td>
<td>improvement</td>
</tr>
<tr>
<td>2009</td>
<td>sheep</td>
<td>n.a. (3)</td>
<td>10</td>
<td>GA95</td>
<td>open</td>
<td>S</td>
<td>silicone and/or PP + HDPE</td>
<td>sealant</td>
<td>PND2</td>
<td>mostly closed</td>
<td>complete tissue coverage</td>
<td>improvement</td>
</tr>
<tr>
<td>2011</td>
<td>sheep</td>
<td>n.a. (3)</td>
<td>7</td>
<td>GA95</td>
<td>fetoscopy</td>
<td>S</td>
<td>silicone</td>
<td>sealant</td>
<td>PND2</td>
<td>mostly closed¹</td>
<td>complete tissue coverage</td>
<td>improvement</td>
</tr>
<tr>
<td>2013</td>
<td>sheep</td>
<td>n.a. (3)</td>
<td>8</td>
<td>GA95</td>
<td>fetoscopy</td>
<td>N + S</td>
<td>collagen and silicone</td>
<td>sealant</td>
<td>PND2</td>
<td>closed¹</td>
<td>complete tissue coverage, less damage to the spinal cord¹</td>
<td>improvement</td>
</tr>
</tbody>
</table>

Size of MMC: values in parentheses are number of vertical lengths. ED = Embryonic day; GA = gestational age (in days); N = naturally derived materials; S = synthetic materials; NA = natural acellular scaffolds; PND = postnatal day; PP = polypropylene; HDPE = high-density polyethylene; n.a. = not available.

¹Results were described, but images were not provided in the paper.
environment, or the construct may be supplemented by the addition of cytokines or growth factors to increase proliferation or optimize differentiation of implanted cells or host tissues as necessary [26]. In many cases, exogenous cells may provide autocrine/paracrine factors to stimulate themselves and endogenous cells to participate in tissue formation. Finally, the scaffold component provides a framework or microenvironment to which implanted cells or host tissues can adhere and proliferate, ultimately replacing missing or damaged tissue. Scaffolds used for tissue engineering have been traditionally categorized into 3 groups: (1) naturally derived materials (collagen, gelatin, hyaluronic acid, fibronectin/fibrin, alginate, chitosan), (2) synthetic materials (e.g. polyactic acid, polyglycolic acid, polycaprolactone) and (3) acellular scaffolds created from human or animal organs treated to remove cells and immunogenic antigens but retaining their original architecture [27–30]. Each of these scaffolds has different biocompatibility, cytocompatibility, biodegradation, and mechanical properties. The choice of utilizing cells and/or scaffolds with or without nutrients is determined by many factors but primarily by the desired tissue end point.

**Experimental Progress in Tissue Engineering for Fetal MMC**

To date, experimental studies of tissue engineering approaches to prenatal repair of MMC can be divided into 2 groups according to the goals of the investigators: (1) to prevent amniotic fluid-induced neural damage by providing coverage of the defect using scaffolds [31–38] and (2) to place a scaffold and/or cells between the neural tissue and the skin repair to prevent adhesion of the repair to the cord (tethering) and/or to provide neurotrophic factors or regenerate neural tissue [39–44].

Several studies have reported promising results with scaffold-based coverage of the MMC defect as an alternative to surgical skin closure to protect the exposed neural tissue, as summarized in table 1. Most studies used the surgically created fetal sheep MMC model, and scaffolds were secured over the defects with either sutures or adhesives by open fetal surgery. For scaffolds, natural materials included collagen or gelatin, synthetic materials included silicone or polypropylene with high-density polyethylene, and one study used acellular small intestinal submucosa. In general, these studies reported complete or near-complete closure of the MMC defect and strongly supported the application of tissue-engineered scaffolds for fetal repair of MMC. However, many of the studies contained significant limitations in study design and execution, making interpretation difficult. In some, the surgically created MMC defects appeared small and inadequate, with the vertebral arches partially intact and the skin and soft tissue defects measuring only 2–3 cm in diameter. Our experience has shown that a defect less than 5 cm in diameter often leads to spontaneous ‘wound healing’ and is associated with inadequate exposure of the spinal cord. In addition, the in utero repair was performed too early in many of the reports, often at the time of MMC creation, essentially making it a wound healing study rather than a study of coverage of an MMC. Finally, one study did not perform histological analyses, and many only described histological results, without photomicrographs to support the claim of successful tissue coverage of the MMC defect. These limitations call into question the validity of the reported results. Further studies using proper MMC models with clear documentation of the histology of the cord and neurological outcomes are needed.

Attempts to augment regeneration or to protect the exposed and damaged spinal cord using scaffolds and/or cells placed between the skin closure and the cord have also been reported and are summarized in table 2. In most, the scaffold was placed using open fetal surgery in the surgically created fetal sheep MMC model. Methodology varied depending on the ultimate aim of the study. For the protection of the neural elements and the prevention of tethered cord, synthetic scaffolds were placed onto the spinal cord as substitute dura mater, and these were immobilized by closure of the skin over the scaffold. For the regeneration of neural tissues, cells were transplanted directly onto the exposed spinal cord or scaffolds (with or without cells) followed by closure of the skin with or without AlloDerm® regenerative tissue matrix (LifeCell EMEA, Kidlington, UK). The reports have been promising, with successful prevention of tethered cord compared to controls, evidence of neo-dura mater formation along the scaffold, incorporation of transplanted cells within the spinal cord, and survival of transplanted cells within the applied scaffold. However, many of the same flaws in study design or execution apply and, in particular, the documentation and characterization of cellular differentiation and integration have been difficult to interpret. It is clear, however, that significant or complete rescue or regeneration of the spinal cord in MMC has not been shown, and further studies are needed to demonstrate functional improvement.
Proof-of-Principle Experiments Induce Formation of Autologous Tissue Coverage of the MMC Defect

Our laboratory has taken the approach of testing and optimizing a variety of scaffolds, cells and growth factors to develop a tissue engineering construct that will ultimately be clinically applicable for prenatal closure of MMC. We have initially tested our constructs using in vitro methods and subsequently applied the constructs to the retinoic acid-induced rat model of MMC using an open fetal surgical technique [31, 32]. Our approach has been that if the construct appears promising in the rat model, which only allows short-term analysis (3 days), we then consider application to the sheep model of surgically created MMC to assess long-term tissue formation.

Initially, we performed pilot studies and elected to use a gelatin-hydrogel construct that released basic fibroblast growth factor (bFGF) over the defect in the retinoic acid-induced fetal rat MMC model [31]. Despite the short interval of evaluation the scaffold demonstrated therapeutic potential with evidence of native fetal tissue migration, epidermal in-growth and neovascularization within and surrounding the scaffold.

We next attempted to confirm the long-term efficacy of the construct utilizing the surgically created fetal sheep MMC model. In this model we could evaluate the construct for approximately 40 days after application to the MMC defect. At 70 days’ gestation, we created a 5-cm MMC defect (extending across 5 lumbar vertebral lengths) large enough to prevent spontaneous closure. At

<table>
<thead>
<tr>
<th>Year</th>
<th>Animal type</th>
<th>Size of MMC at creation</th>
<th>Animals, n</th>
<th>Timing of repair</th>
<th>Method</th>
<th>Aim</th>
<th>Scaffold type</th>
<th>Scaffold Cell type</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007 sheep n.a. (4)</td>
<td>4</td>
<td>GA100</td>
<td>scaffold placement between neural tissue and closed skin</td>
<td>prevent tethered cord</td>
<td>NA</td>
<td>acellular dersis</td>
<td>GA140</td>
<td>abnormal adhesion of neural tissue to the scaffold</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008 sheep n.a. (4)</td>
<td>8</td>
<td>n.a. (14–25 days after MMC creation)</td>
<td>MMC closure with AlloDerm and direct injection of NSC into gray matter</td>
<td>enhance neural development</td>
<td>NSC</td>
<td>PND1</td>
<td>survival of cells in undifferentiated stage, functional improvement</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011 sheep n.a. (4)</td>
<td>2</td>
<td>GA100</td>
<td>scaffold placement above and below closed dura</td>
<td>regenerate neural tissues</td>
<td>S</td>
<td>cellulose</td>
<td>GA138</td>
<td>no adverse effects, unknown potential of regenerated neural tissue</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012 sheep 3 × 2 cm (3)</td>
<td>3</td>
<td>GA90–93</td>
<td>scaffold placement between neural tissue and closed skin</td>
<td>prevent tethered cord</td>
<td>S</td>
<td>cellulose</td>
<td>GA132</td>
<td>scaffold incorporation into neo-dura mater without abnormal adhesion</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013 sheep n.a.</td>
<td>2</td>
<td>GA100</td>
<td>placement of scaffold seeded with h-iPS-derived NCSC with hydrogel between neural tissue and closed skin</td>
<td>regenerate neural tissues</td>
<td>S</td>
<td>PLLC and PG</td>
<td>h-iPS derived NCSC</td>
<td>10 days before term</td>
<td>survival of differentiated cells, integrated into native spinal cord</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>2014 sheep n.a. (5)</td>
<td>4</td>
<td>GA100</td>
<td>scaffold placement between neural tissue and closed skin</td>
<td>protect spinal cord</td>
<td>N</td>
<td>amniotic membrane</td>
<td>GA135–145</td>
<td>better preserved spinal cord with less abnormal adhesion, wound dehiscence</td>
<td>44</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Size of MMC: values in parentheses are number of vertical lengths. n.a. = Not available; GA = gestational age (in days); NA = natural acellular scaffolds; S = synthetic materials; N = naturally derived materials; PLA = poly-L-lactic acid; PLLC = poly-L-lactide-cocaprolactone; PG = polypropylene glycol; NSC = neural stem cell; h-iPS = human-induced pluripotent stem cell; NCSC = neural crest stem cell; PND = postnatal day.
100 days’ gestation, gelatin-based composites combining sponges and sheets were applied to cover the defect and secured with adhesive, obviating the need for separate skin closure. The animals were harvested at 140 days’ gestation, and histological evaluations were performed (fig. 1a–g).

Interestingly, the process of tissue regeneration induced by the gelatin scaffolds mimicked the phases of proliferation and remodeling well described in the wound healing process. Migration of local fibroblasts, re-epithelialization from the wound edges and neovascularization, all of which are consistent with the proliferative phase of wound healing, were observed at the level of the MMC 2 weeks after the tissue-engineered in utero repair. These processes continued to mature without any adverse effects, resulting in newly formed tissue coverage over the

Fig. 1. Representative images and associated schematic diagrams of the MMC defect at creation (a), with applied tissue-engineered repairs (b–d) and upon harvest at term (e). Upper a–e Schematic diagrams of the MMC defect depict the exposed neural tissue (black), the open vertebral canal (gray), the sponge scaffold (dot pattern), and the gelatin-based sheet (dashed line). Lower a–e Representative photographs of an MMC defect from creation to repair to harvest. a An MMC defect created at 72 days’ gestation. The skin and soft tissue defect measured 5 cm in diameter. The vertebral arches have been resected to leave an open vertebral canal with a fully exposed spinal cord extending across 5 vertebral lengths. b An MMC defect at 100 days’ gestation before application of tissue-engineered repair. The skin and soft tissue defect has shrunk in a typical fashion, especially in the lateral aspect, to measure 3.2 × 1.8 cm. Only the remnant spinal cord remains exposed and has a flattened, stretched and separated ‘hemi-cord’ appearance. c An MMC defect with an overlying sponge scaffold treated with growth factor solution. The sponge was trimmed to fit the size of the defect at the time of application. d An MMC defect with sponge scaffold and flexible sheet. The sheet was secured to the fetal skin with cyanoacrylate adhesive. e An MMC defect at the time of harvest at 140 days’ gestation. In this animal the sheet had become detached between the time of repair and the time of harvest, but the sponge scaffold appears to have been incorporated into the defect. Of particular interest is the appearance of blood vessels in the area of the sponge, with evidence of neovascularization confirmed on histological analysis. f A representative transverse section with HE staining through the MMC defect with tissue-engineered repair, with sustained release of bFGF at 140 days’ gestation. Magnification ×5. The ‘hemi-cords’ are marked by solid triangles. g HE-stained sections across the center of an MMC defect in the same animal. Magnification ×20. Box bracket delineates the sponge over the spinal cord. Mature granulation tissue (solid star) with collagen deposits is also evident beneath multiple epithelial layers (open star).
MMC defect by the time of harvest at term. Scaffolds treated with bFGF promoted improved coverage of the MMC defect compared to scaffolds without bFGF, with more mature, consistent granulation tissue and epithelial tissue across the entire defect (fig. 1f, g). On histological sectioning, scaffolds containing bFGF demonstrated better preservation of the spinal cord, with less associated damage to the white matter compartment. These experiments provide important proof-of-principle support for the efficacy of material-based tissue-engineered coverage for prenatal treatment of MMC. Preservation of the spinal cord was still incomplete, however, and further optimization of a less invasive approach is needed.

**Experimental Progress in the Development of a Minimally Invasive Approach for Prenatal Closure of MMC**

Several papers have been published focusing on the development of a minimally invasive approach in fetal surgical repair for MMC in order to decrease the risk of neural injury by early gestation MMC closure as well as to decrease the associated maternal and fetal risks [37, 38, 45]. All studies to date have applied scaffolds via fetoscopy with or without maternal laparotomy, and most have performed their interventions in the surgically created sheep model. The scaffolds, either synthetic or naturally derived materials, were secured with suture or adhesives. The number of trocars varied from 1 to 4 and the size of trocars also varied from 2 to 8 mm. In general, a tendency towards the use of fewer and smaller trocars was noted. Complications were also varied; in most, sustained amniotic fluid leakage from trocar sites was observed. However, premature labor, premature rupture of membranes or fetal demise, which were often observed clinically after fetoscopic MMC repair [17, 18, 46], were not noted in sheep experiments due to the quiescent sheep uterus. Peiro et al. [38] recently reported success in repairing MMC in uterus in the fetal sheep model using single trocar (2.7 mm) fetoscopy in a low-pressure amniotic cavity carbon dioxide environment by placing a collagen patch and securing it with COSEAL® Surgical Sealant (Baxter International, Deerfield, Ill., USA). They report universal success with ‘a normal appearing spinal cord covered with newly formed dura mater’ and reversal of the Arnold-Chiari malformation. Unfortunately, they show no histology or imaging, do not demonstrate how the absence of Arnold-Chiari was determined and do not provide other details. As a correctly made sheep MMC defect results in histological abnormality of the spinal cord even (when repair is performed) and incision of the central canal of the cord (which they do not describe) is required in the sheep model to induce the hindbrain herniation component of the Arnold-Chiari malformation [10, 47], the results of this laboratory need to be confirmed. Further studies using proper MMC models are needed. Fetoscopic technique with the use of fewer and smaller trocars will undoubtedly be a component of successful MMC closure in the future.

**Future Challenges**

In utero repair of MMC using tissue engineering techniques has been more difficult than anticipated because of the unique challenges that the fetal environment presents. The fetal environment contains several biological advantages that favor a tissue-engineered approach, such as the existence of a high frequency of endogenous highly proliferative stem cells in various fetal tissues and the amniotic fluid [25, 48–50], the potential for scarless wound healing [51] and the relatively small size of the fetus. However, at present, these advantages are outweighed by several disadvantages that limit tissue engineering in the fetus. The surrounding fluid environment presents difficulties with visualization for procedures and prevents adherence of scaffolds or constructs. The limitations described above related to fetoscopic suturing of gelatinous fetal skin make tissue adhesives a logical choice for securing a construct to the MMC defect. Unfortunately, there are no adhesives that will reliably adhere with underwater application. The use of adhesives is also complicated by the exponential growth of the fetus and rapid turnover of the skin epithelium. It is likely that nonexpansible or rigid materials that are glued to fetal skin will tear free or shed before tissue coverage can be established. These limitations have prompted the use of uterine insufflation to provide a clear and relatively dry environment for surgical manipulations. However, the safety of uterine insufflation has not been rigorously tested. Finally, conventional fetoscopic surgical techniques to apply tissue-engineered constructs or to surgically close the MMC, when performed at the same gestational age as open fetal surgery is currently performed, is an incremental step forward at best. Fetoscopic procedures, particularly when multiple trocars and prolonged operating times are required, have not demonstrated improved maternal or fetal safety over open fetal procedures and have proven less reliable for closure of the defect. A true paradigm-chang-
ing prenatal therapy for MMC would be applicable by ultrasound-guided injection or by single-port fetoscopy at much earlier gestational time points, ideally by 15–18 weeks’ gestation. It would incorporate tissue engineering principles of an injectable scaffold of biocompatible material that would be secured over the MMC defect by either adhesive or sheet application or both. It would potentially contain growth factors to stimulate endogenous stem cell activity and provide neurotrophic or protective activity. Finally, it would generate a fluid-impermeable tissue layer without adherence to the underlying neural placode. This is a challenging ideal but can conceivably be accomplished with current technology and should be the ultimate goal of investigators in this field. This will require multidisciplinary collaborations between fetal therapists, tissue engineers, stem cell biologists and probably other expertise to develop creative solutions to the current challenges in prenatal surgical repair of MMC. Only when a new technique has been proven experimentally should well-designed clinical studies be pursued that compare the new technique to the established standard of open fetal surgical repair.

References


