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Review

Laminin therapy for the promotion of muscle regeneration

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ABSTRACT

Muscle regeneration is essentially due to activation of satellite cells, which can be isolated and amplified ex vivo, thus representing good candidates for cell therapy. Accumulating data show that the local microenvironment plays a major role during muscle regeneration. In the satellite cell niche, a major extracellular matrix protein is laminin. Human myoblasts transplanted into immunodeficient mice are preferentially located in laminin-enriched areas. Additionally, laminin-111 enhances myoblast proliferation in vitro and increases expression of the α7β1 integrin-type laminin receptor. Intramuscular injection of laminin-111 ameliorates muscular pathology in mdx mice, protecting muscle fibers from damage. Moreover, transplantation of human myoblasts with laminin-111 into Rag/mdx immunodeficient recipients improved efficacy of myoblast transplantation, increasing the number of human dystrophin-positive myofibres. Taken together, these data strongly indicate that exogenous laminin can ameliorate the regeneration process in different models of muscular dystrophies and can be instrumental for improving cell therapy aiming at repairing the degeneration/regeneration process in skeletal muscle.

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1. Introduction

Muscle regeneration is essentially due to the activation of rare unipotent muscular stem cells, called satellite cells (SC), which are located in a specific niche, between the basement membrane (BM) and the sarcolemma of muscle fibers [1]. After trauma or injury, SC are activated, enter into the cell cycle, and undergo proliferation. This initial proliferative phase is followed by differentiation and muscle regeneration, which occurs by the fusion of myoblasts either among themselves, forming new myotubes, or fusing with existing damaged fibers. SC in healthy skeletal muscle are quiescent and express the paired box protein Pax7. They also express other surface markers such as c-met and CD56 (N-CAM) [2,3]. Depending on the nature of the stimulus (trauma, injury or diseases), the hepatocyte growth factor binds c-met and activates the SC's [4,5], which then upregulate their expression of Myf5 and MyoD, two of the myogenic regulatory factors (MRF) expressed early after c-Met activation, and then myogenin and Mrf-4, essential for terminal differentiation, with the formation of post-mitotic multinucleated myotubes, although MRF-4 may also play a role during development. These MRF induce the SC cells to differentiate after the phase of proliferation. For example, MyoD induces myoblasts to exit the cell cycle by enhancing the P21 transcription factor, while myogenin triggers the expression of genes involved in differentiation [6]. A sub-population of SC undergo asymmetric division during the early phase of regeneration, and will restore the pool of precursors [7]. Satellite cells are the only progenitors physiologically able to regenerate adult skeletal muscle after injury [8].

In this review, we will define the proliferating SC (expanded in vitro or in vivo, after activation and before fused into myotubes) as myoblasts. Given that these cells retain the muscular regenerative capacity throughout the life span, and since they can be readily isolated and amplified ex vivo, they have been envisioned as good candidates for cell therapy: during muscle regeneration ex-vivo repaired (autografts) or normal (allografts) cells may be inserted into a dystrophic muscle to restore the missing protein (e.g. dystrophin in the case of Duchenne Muscular Dystrophy-DMD).

Although optimistic results were obtained by myoblast transplantation in animal models, clinical trials, which started in the 90s, failed to show any clinical benefit. Despite the progress in

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our knowledge of muscle stem cell biology accumulated over the years, no clear-cut benefits for the patients have been shown so far [9,10], and improvements for cell therapy are necessary.

The fact that the injected myoblasts do not fulfill their expected function efficiently when injected into patients, is an important issue that needs to be explored. The results obtained from animal models and in clinical trials using myoblasts as the cell source to be grafted, have already highlighted some of the hurdles involved: cell death, limited proliferation and migration of the transplanted myoblasts, and the immune response against the donor cells in allografts [2,11–13]. Interestingly, freshly isolated SC present a much more efficient regenerative capacity than myoblasts amplified in culture [14]. Since in vitro amplification is necessary to obtain the necessary numbers of cells prior to cell therapy, improvement in cell culture conditions is essential [10].

The injection site where cells are to be transplanted also needs to be considered in myoblast transfer therapy. Once transplanted, myoblasts will be in contact with a local microenvironment that is ultimately able to modulate their fate. Previous data show that this microenvironment plays a major role during muscle regeneration, by modulating the muscle progenitors and their interaction with other cell types present during tissue regeneration. The muscle microenvironment includes extracellular matrix (ECM) molecules, secreted factors produced by either muscle progenitors themselves, or differentiated/regenerating fibers, or also by non-muscle cells such as fibroblasts and/or inflammatory cells present in dystrophic or degenerating muscle. Cell fate, such as differentiation *versus* proliferation, or self-renewal, will be the result of multiple interactions that will end up modifying the environment and eventually the epigenetic status of the target cells. Modifications observed in conditions such as aging or muscular dystrophy, disturb the subtle balance between the cell compartments that ensure proper tissue function and repair, leading to impaired regeneration and fibrosis [15,16]. Considering the issues briefly discussed above, it is obvious that improving the pre-transplantation culture and injection conditions, as well as increasing our understanding of the regenerative microenvironment where muscle differentiation takes place, will provide essential clues to ameliorate the efficiency of this strategy.

2. Laminin and basement membrane

LM is a major component of the BM and comprises a glycoprotein family with a cross-shaped structure. In vertebrates five alpha (α) chains, three beta (β) chains and three gamma (γ) chains have been identified [17]. Alpha, beta and gamma chains combine to form heterotrimeric isoforms, with a molecular weight between 400 and 900 Da. Presently, eighteen LM isoforms have been described, although the in vivo existence of some of them still needs to be confirmed [18]. These isoforms are named according to their chain composition [19]: for example, the LM 111 (LM-111) is composed of the α1, β1 and γ1 chains.

Laminins are widely distributed throughout the body, mainly in BM, playing important roles in tissue structure and maintenance, cell signaling, adhesion, migration, among other functions [20,21]. Each LM isoform is differently expressed in the body. For instance, LM-211 and LM-221 have been identified in the neuromuscular system, whereas LM-332 is the most abundant isoform in the skin. LM isoforms containing α4 chain are the major isoform present in the BM of blood vessels and the isoforms-containing α5 chains are widely distributed through the body. LM-111, despite being the most studied isoform, is restricted in adults to some epithelial BM [22].

In the skeletal muscle tissue, LM short arms essentially play a structural role, interacting with other LM short arms, thus creating a network where type IV collagen binds LM via entactin/nidogen, thus structuring the muscular BM. Adhering to this initial BM, other ECM components, such as collagens and proteoglycans, will form the interstitial matrix [23]. The long arm of the LM cross is an α-helical coiled coil structure composed of the three chains. The C-terminal part of the α chain extends into the long arm and has 5 LM G-like domains, representing a very important binding site for cell surface receptors. Cell–LM interactions are mediated by integrin-type as well as non-integrin receptors, including dystroglycan, syndecans and lutheran blood group glycoprotein. The integrins α1β1, α2β2, α3β1, α6β1, α6β4, α7β1, α9β1, αvβ3, αMβ2 are known to bind LM, and most of them recognize the globular domain of the long arm [20,22,24]. However, only four of these integrins are considered to be highly selective LM receptors: α3β1, α6β1, α6β4 and α7β1 [25–27].

3. Laminin in normal skeletal muscle and regeneration

As mentioned above, LM are major BM components, and LM-211 and LM-222 are the main isoforms present in adult skeletal muscle, linking muscle fibers and SC to other BM components such as collagens, glycoproteins, proteoglycans and glycosaminoglycans [23]. LM-211 is located within the BM that surrounds the sarcolemma, whereas LM-221 predominates in the neuromuscular and myotendinous junctions [28]. The importance of these α2-containing LM isoforms is emphasized by the fact that mutations in the α2 LM chain causes severe congenital muscular dystrophies in both humans and animals [29]. The muscle fiber binds to LM via two major receptors: β-dystroglycan [30] and the integrin α7β1 [31]. During skeletal muscle regeneration, LM isoforms in addition to LM-211 and LM-221 are also expressed. For example during the regenerative process induced by crush injury in normal and in dy/dy mice (a mouse model for the LM alpha 2 mutation), α4 and α5 LM chains are transiently expressed in the BM of small diameter myofibers (that correspond to the newly regenerated muscle fibers), suggesting their involvement in early myogenic differentiation. α4 and α5 LM chains are also present during the early fusion process [32] in regenerating muscles of BALB/c mice. Alpha-7 integrin chain can also be detected in myoblasts and newly formed myotubes. In the dy/dy mouse, α6 integrin chain is also detected in the newly formed myotubes [33].

In DMD patients and in mdx mice (the mouse model for DMD) α7 integrin chain is upregulated, while the levels of this molecule are reduced in patients with LM α2 chain congenital muscular dystrophy and in dy/dy mice [34]. The increase in α6 integrin chain observed in the newly formed myotubes of dy/dy mice may potentially compensate the decrease in α7 or the absence of α2. Moreover transgenic overexpression of α7 integrin chain in α2 LM chain deficient mice reduces muscle pathology [35]. These results indicate that although LM-211 and the integrin α7 (together with the dystroglycan complex) predominate in the BM of muscle fibers, other LM isoforms and other integrins are modulated during regeneration, suggesting that these molecules also play a relevant role during muscle repair.

4. Laminin in myoblast transplantation

In an ideal configuration for cell therapy to ensure efficient repair, the transplanted myoblasts will survive, proliferate and migrate substantially before differentiating and ultimately regenerate the damaged muscle. In addition, a pool of "healthy" SC must be created to ensure "future" cycles of regeneration. Since LM can protect different cell types from death, promote proliferation and migration and influence differentiation, the various LM isoforms

may represent important tools in protocols aiming to improve cell therapy for muscular diseases.

Using a model where human myoblasts were transplanted into damaged and/or irradiated *tibialis anterior* muscle of immunodeficient mice, we demonstrated that injected myoblasts were preferentially located in LM-enriched areas. The regenerative capacity of human myoblasts transplanted into irradiated and cryodamaged muscles was higher, as compared to muscles that were only cryodamaged. Local irradiation increased muscular LM deposition, as well as the number of donor cells and most importantly, the number of human fibers one month after transplantation [36]. More recently, we showed that LM (detected with a polyclonal antibody that does not discriminate a particular isoform) is present at the site where human myoblasts were injected into damaged *tibialis anterior* muscle as early as the first hours after transplantation, forming "pocket-like" structures where transplanted cells were concentrated. This expression was increased as a function of time post-transplantation [13]. However, despite the increase of LM deposition within these pockets, the proliferation rate decreased and cell migration stopped as early as 3 days post-injection, a time point when differentiation was observed, indicating that the LM present around the cells was not sufficient to stimulate the proliferation and dispersion of the injected human myoblasts.

As discussed above, the major hurdles hampering the success of myoblast transplantation are a rapid cell death, a low proliferation of the transplanted cells and, possibly linked to the former, a reduced migration within the host's tissue [11,37]. LM can trigger cellular signals, potentially influencing processes such as survival, proliferation and migration [22,38]. This is also true concerning SCs and myoblasts: LM stimulates cultured myoblasts to survive, proliferate and migrate [36,39–44].

5. Exogenous LM treatment improves muscle regeneration and efficiency of myoblast transplantation

In vitro, treatment with LM-111 increased α7 integrin expression in murine and human DMD patient myoblasts. Moreover, intramuscular injection of LM-111 increased α7 integrin in muscle fibers and ameliorated the dystrophic phenotype in mdx mice. LM α1 chain was still detected in the BM of muscles from mdx mice 28 days after intra-peritoneal injection of this isoform in ten-day-old mdx pups. This systemic LM-111 treatment resulted in an important reduction in serum creatine-kinase levels in mdx mice after 3 weeks [45]. It was also demonstrated that both intramuscular and intraperitoneal LM-111 injection protected muscle fibers of mdx mice from damage induced by eccentric contractions [40]. Finally, the transplantation of human myoblasts with LM-111 in *tibialis anterior* muscles of Rag/mdx mice improved the efficiency of myoblast transplantation, with more human dystrophin-positive myofibers 24 days after grafting [40].

When a large number of, myoblasts are injected, concentrated within adapted medium, they cannot anchor with ECM, and this may lead to anoikis, a programmed cell death secondary to cell displacement from ECM [46]. Human myoblasts cultured in conditions preventing adhesion showed an important percentage of apoptotic cells (anoikis), and the addition of fibronectin diminished significantly this percentage. When human myoblasts were injected together with fibronectin in immunodeficient mice, the presence of this molecule significantly increased the survival of injected cells as compared to those injected without fibronectin [47]. This raises the hypothesis that injection of myoblasts with LM may also somehow nurse the cells in the first hours after transplantation, although this still needs to be demonstrated.

Treating α2 LM chain deficient (dy^w) mice with LM-111 resulted in a reduction of the muscle pathology, in parallel with an increased lifespan. The injected LM-111 isoform could be identified within the ECM surrounding the muscle fibers. One possible mechanism explaining the positive effect of LM is apoptosis reduction, since TUNEL-positive muscle nuclei were decreased in LM-111 treated animal when compared to the group treated with PBS. Interestingly, primary myogenic cells isolated from α2 LM (also called merosin) deficient congenital muscular dystrophy type 1A (MDC1A) patients, presented a reduced apoptosis when treated with murine or human LM-111, indicating that the LM-111 effect is conserved between mouse and human [48]. The same group also observed that an improved regeneration of the muscles of dy^w mice was observed after injection of LM-111 (with an increase in numbers and size of myofibers), resulting in enhanced expression of myogenin, embryonic myosin heavy chain and α7β1 integrin, and overall an improvement of muscle regeneration [49].

α7 integrin chain deficient mice present defective muscle regeneration and a reduced expression of α2 LM chain in the BM of their muscle fibers [50]. In these animals, α1 LM chain could be detected surrounding the muscle fibers after LM-111 treatment, which restored muscle regeneration [51].

It is important to note that LM treatment can also influence other cell types distinct from muscular progenitors. LM-111 treatment, 1 week before eccentric exercise, resulted in an increase in the number of proliferating SC, but also in a decrease in gene expression of proinflammatory cytokines by muscle-derived mesenchymal stem cells [52].

6. Conclusions and perspectives

The data summarized above strongly indicating that LM plays a role in the survival, proliferation and dispersion of transplanted human myogenic precursors suggest that manipulation of LM-mediated interactions can be envisaged as a strategy for improving cell therapy in skeletal muscle degeneration/regeneration processes, as illustrated in Fig. 1. However, a detailed knowledge of which myogenic precursor-derived genes are transcribed or repressed along with or because of such interactions are lacking, and a better understanding of the complex signaling underlying this whole process, including identifying parameters involved in the progression of the dystrophic process, which in turn may represent therapeutic targets, is essential.

Another important issue to consider is the large variety of LM isoforms. So far, only LM-111 has been applied in cell therapy protocols in regenerating skeletal muscle tissue, and we do not know if other isoforms may be more efficient than LM-111. Knowing which LM isoforms are expressed over time following myoblast transplantation would be instrumental, in order to better design experiments using other isoforms as adjuvant in myoblast therapy experiments.

Both cell and gene therapy approaches are hampered by the difficulty to reach the targets within a dystrophic and fibrotic tissue, and a modified LM network may play a relevant role in these processes. We hypothesize that disturbances in the complex signaling networks regulating LM are involved, at least partly, in the development of fibrosis, which is a major pathological event in the evolution of muscle dystrophies, and which gradually blocks access to or dispersion of transplanted cells applied as a therapeutic strategy.

In terms of translating the experimental data into therapeutic protocols to be applied in humans, a further important step to overcome is the immune response of the host. As we described above, in human-mouse xenograft models used for transplanting human myogenic precursors, the recipients are immunodeficient animals, unable to elaborate a cell-mediated immune response. In mouse/mouse models, isogeneic transplantation conditions are

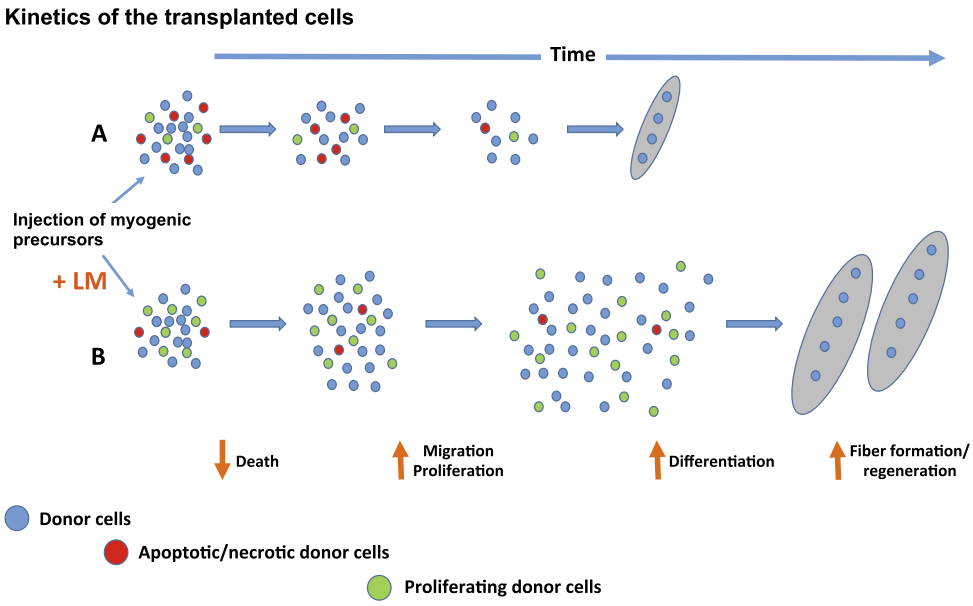

Fig. 1. Hypothetical role of laminin as a therapeutic co-factor for improving cell therapy in muscular lesions. The diagram shows in A the fate of the transplanted myogenic precursors after injection*. Among the population of transplanted myoblasts (blue cells), many cells die, but some proliferate. At later time points after transplantation, proliferation decreases, as well as cell death. Cells reach proliferative arrest and differentiation, correlated with a poor dispersion. In line B we hypothesize that co-injection of myoblasts with laminin (LM) may enhance early myoblast survival in the first hours post-engraftment, probably avoiding anoikis. LM can also increase proliferation and migration, and consequently delay myoblast differentiation, which will result in bringing a therapeutic effect to a larger area of the damaged muscle. *Line A was based on Ref. [12].

usually used, again bypassing the adaptive immune response issue. Ongoing experiments in our laboratory indicate that we can induce immunological tolerance to human myoblast antigens in immunocompetent recipients. This will hopefully allow us to further study the expression and role of LMs in pre-clinical settings for cell therapy aiming to regenerate skeletal muscle in humans.

Despite the promising effects of exogenous LM in experimental animal models of muscular diseases, alone or as co-adjuvant in cell therapy, some aspects need to be taken into account before translating this approach for patients. A source for clinical grade purified laminin has to be defined: LMs can be produced as recombinant proteins, but since they are large (LM-111 has around 900 kd) and heterotrimeric, their large scale production may represent a technological as well as an economic challenge.

Another issue to be taken into consideration is the putative immune reaction against the LM applied. In the papers we have discussed, the LM used for therapy was the natural LM-111 purified from Engelbreth–Holm–Swarm mouse sarcoma cells. In some studies, this LM was incorporated in the BM of muscle fibers 1 month after treatment [51,49,45], indicating the absence of an adaptive immune response against the molecule, but more detailed studies are required. As an alternative strategy LM-derived peptides or fragments could be used, since they are easy to be isolated and produced, potentially much less immunogenic, and their potential has been documented [53,54], although not in terms of clinical benefit: an intact LM molecule may be necessary to restore the BM structure.

In conclusion, further understanding of the LM biology in muscle regeneration, together with the definition of which are the conditions to optimize its usage in cell therapy for skeletal muscle, represent new challenges to be overcome.

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