Rapid and Complete Recovery of Responsiveness to Adenosine and Norepinephrine by Regenerating Arterioles of the Tibialis Anterior Muscle of the Hamster After In Situ Autografting

Louis M. Messina and Bruce M. Carlson

Intravital microscopy studies of small bundles of fibers of the extensor digitorum longus muscle grafted onto the hamster cheek pouch revealed a persistent reduction in the responsiveness of regenerated arterioles to vasoactive agents. We tested the hypothesis that the recovery of responsiveness to vasoactive agents by regenerating arterioles within whole, in situ autografted tibialis anterior muscles occurs earlier and more completely than that reported for regenerating arterioles within bundles of fibers of the extensor digitorum longus muscle grafted ectopically to the hamster cheek pouch. The tibialis anterior muscles of Syrian golden hamsters were excised and soaked in bupivacaine (0.75%) for 10 minutes to ensure uniform degeneration of muscle fibers. The tendons were resutured, and the graft became revascularized spontaneously. Fluorescent intravital microscopy was used to measure the responsiveness of 10-40-μm arterioles to topically applied adenosine and norepinephrine at 7, 14, and 30 days after grafting. Nine to 25 arterioles were studied at each time period. Both intravital and light microscopy were used at each time period to characterize the structural development of the microcirculation. We found that the responsiveness of regenerated arterioles returned to control values for topically applied norepinephrine by 14 days and for adenosine by 30 days. Light microscopy showed regenerated blood vessels in the center of the grafts early in the second week after grafting. The structure of the microcirculation at 7 days was characterized by a plexiform microvascular pattern, long spiderlike capillaries, and arterioles and venules that had irregular walls and an irregular branching pattern. Rhodamine-labeled albumin extravasated spontaneously. The 14-day grafts had a more linear capillary pattern, and the arterioles and venules often contained loops that had circular flow patterns. By 30 days, a parallel capillary structure had developed, no vascular loops were present, and the arteriolar-venular pattern was nearly normal. We conclude that recovery of responsiveness to vasoactive agents by regenerating arterioles within whole, in situ autografted tibialis anterior muscles occurs earlier and more completely than that reported for regenerating arterioles within bundles of fibers of the extensor digitorum longus muscle grafted ectopically to the hamster cheek pouch. These results suggest that the intactness of the microcirculation at the time of initiation of regeneration and the local environment may have substantial effects on the nature and extent of regeneration.

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Much of our knowledge concerning the process of regeneration of a microcirculation is based on observations of the regeneration of small pieces of tissue that have been transplanted to ectopic sites, such as the hamster cheek pouch,1,2 the chorioallantoic membrane of the chick embryo,3 or a rabbit ear chamber.4 However, the process of regeneration of a microcirculation within these small pieces of tissue transplanted to ectopic sites may be quite different from the process that occurs when an intact, whole organ or muscle regenerates in situ. One reason is that during in situ regeneration of a whole muscle, the microcirculation is not disrupted mechanically at the time of grafting.
In addition, there might be important differences in the rate of regeneration of various tissues depending on the site of grafting.

For example, intravital microscopy studies of small bundles of fibers of the extensor digitorum longus (EDL) muscle grafted onto the hamster cheek pouch revealed persistent abnormalities in the responsiveness of regenerating arterioles to vasoactive agents. No vasodilator response of the regenerating arterioles to topically applied adenosine was observed until 60 days after grafting. The response of the regenerating arterioles to adenosine remained subnormal even at 180 days after grafting. Even greater differences were seen in the response of regenerating arterioles to the vasoconstrictor norepinephrine. No response of the regenerating arterioles to norepinephrine occurred until 90 days. Between 90 and 120 days, only small segments of the arterioles constricted. By 180 days, the vasoconstrictor response was uniform along the arteriolar wall but still diminished from normal.

We developed a model of regeneration of a microcirculation of a whole, intact skeletal muscle whereby the tibialis anterior muscle of the Syrian golden hamster was autografted in situ. After autografting, the muscle underwent ischemic necrosis and subsequent regeneration. We tested the hypothesis that the recovery of responsiveness to vasoactive substances by regenerating arterioles of the in situ autografted tibialis anterior muscle occurs earlier and more completely than that reported for regenerating arterioles within bundles of fibers of the EDL muscle grafted ectopically to the hamster cheek pouch. In addition, we assessed the structural and histological process of regeneration of the microcirculation using both intravital fluorescent and light microscopy.

Materials and Methods

Preparation

Syrian golden hamsters weighing between 90 and 100 g were anesthetized with sodium pentobarbital (0.1 mg/g body wt). Both hind legs were shaved and swabbed with a betadine solution. Autografting of the tibialis anterior muscle was begun by incising the muscular portion of the biceps femoris muscle parallel and lateral to the tibialis anterior muscle. This lateral incision minimized scarring between the muscle and the overlying biceps tendon during regeneration. The tendinous portion of the biceps femoris muscle was reflected medially, exposing the tibialis anterior muscle. The distal tendon of the tibialis anterior muscle was transected, and then the planes between the tibialis anterior muscle and the EDL muscle as well as the tibia were incised sharply. Finally, the insertion of the tibialis anterior muscle onto the proximal tibia was transected. The muscle was soaked in bupivacaine (0.75%) for 10 minutes to ensure uniform degeneration of skeletal muscle fibers. The muscle was returned to its original bed, and the tendons were resutured to the proximal and distal stump with 6-0 prolene. The overlying skin and muscle were approximated with 5-0 interrupted prolene sutures. In each hamster, both tibialis anterior muscles were grafted. One to three arterioles were studied per graft. The hamsters were observed until they had fully recovered from the effects of anesthesia and were then returned to their cages.

At different time intervals after grafting, the pattern of the microcirculation and the responses of regenerating arterioles of the tibialis anterior muscle to vasoactive agents were examined. Hamsters were prepared for these examinations as follows. After the hamsters were reanesthetized with sodium pentobarbital, the right carotid artery and the left jugular vein were cannulated, and a polyethylene endotracheal tube was inserted into the trachea. The hamsters were transferred to the stage of a Wayland-Frasher intravital microscope. To maintain continuous anesthesia, a constant infusion (0.0078-0.0130 ml/min) of sodium pentobarbital (9 mg/ml) was given through the cannula in the jugular vein. The polyethylene endotracheal tube was connected to a T-shaped connector, and the hamster breathed spontaneously a mixture of 30% O2-70% N2. Arterial blood gases were obtained to ensure that the PO2 was maintained between 75 and 100 mm Hg. A rectal temperature probe was placed and connected to a servocontrolled heating pad, which maintained rectal temperature at 37°C. Either the right or left lower leg was then fixed to a Plexiglas platform in a horizontal plane (Figure 1). The skin and tendinous portion of the biceps femoris muscle were incised directly over the tibialis anterior muscle. At all times after exposure of the muscle, it was bathed in a suffusate that had a millimolar composition of NaCl 130.9, KCl 4.7, CaCl2 2.0, MgSO4 1.2, and NaHCO3 20.0. The flow rate of the suffusate (5 ml/min) was adjusted to provide a temperature of ~35°C over the muscle. The temperature was measured frequently throughout the procedure with a beaded thermistor probe inserted directly into the suffusate over the muscle. The suffusate was equilibrated with a gas containing 5% CO2 to maintain the pH between 7.38 and 7.42.
After an equilibration period of 50 minutes, bovine serum albumin (Sigma Chemical Co., St. Louis) conjugated to rhodamine-B (excitation, 567 nm; emission, 584 nm; Molecular Probes, Eugene, Ore.) was given intravenously into the jugular vein in a volume of 0.2 ml for 1 minute. The preparation was illuminated with a 100-W mercury lamp (Wild Leitz Inc., Cincinnati, Ohio) connected to an incident light illuminator (American Optical, Buffalo, N.Y.) (Figure 1). The light passed first through an excitation filter (546 nm) and second through a dichroic mirror (560 nm) and was then reflected back through a barrier filter that transmitted light above 515 nm to a relay lens and subsequently to the television camera. Two heat filters (model KGB12, Leitz) were used; they also functioned as neutral density filters (5% each) and removed all wavelengths <450 nm. A×10 American Optical objective (numerical aperture [N.A.]=0.25), a×20 immersion objective (N.A. =0.33, Nikon Inc., Garden City, N.Y.), and a×25 Leitz long-working distance objective (N.A. =0.40) were used. A closed-circuit video system, which consisted of a Dage SIT model 66 video camera (Dage-MTI, Inc., Michigan City, Ind.), a Panasonic four-head VHS videocassette recorder, and a Panasonic 12-in. high-resolution video monitor, was used to view the microcirculation.

Each exposure of the muscle to the light was limited to between 30 and 120 seconds to minimize light-induced changes in the microcirculation. In control muscles, light-induced effects were most commonly manifested by the initiation of vasoconstriction or by persistent vasoconstriction. Reaction to light was observed only rarely in the transplanted muscles.

**Experimental Protocol**

Within normal tibialis anterior muscle, which served as the control, or within regenerating tibialis anterior muscle grafts, responsiveness of arterioles to the topical application of norepinephrine (10⁻², 5×10⁻³, and 10⁻⁴ M) and adenosine (10⁻³, 10⁻⁴, and 10⁻⁵ M) was assessed by measuring the diameter of arterioles. Muscle grafts were studied at 7, 14, and 30 days after in situ autografting. The appropriate concentrations of the vasoactive agents were achieved by adding adenosine and norepinephrine to the suffusate reservoir. The arterioles were recorded on videotape 2 minutes after exposure of the vasoactive agent. The order in which these concentrations were applied was varied randomly between hamsters. The vessels lost their reactivity sometimes for as long as a half hour after the application of norepinephrine; therefore, in more than half the experiments, the randomized doses of adenosine were applied before the doses of norepinephrine. The reservoir was flushed thoroughly between different concentrations of the vasoactive substances. The arteriole was allowed to return to its original diameter between applications.

Changes in arteriolar diameter were observed on a high-resolution video monitor and recorded on a videotape. During playback of the videotape, the diameter of the arterioles was measured with calipers when the border of the column of fluorescent plasma was at its sharpest and at its widest diameter. The percent change in diameter was determined from the ratio of change in diameter to the initial diameter. The dimensions measured were calibrated by measuring the video image of a stage micrometer (Graticules, Ltd., Tonbridge, Kent, UK) during video playback.

At the completion of the concentration–response studies, a survey of the entire surface of the microcirculation was made at ×300 magnification. After this procedure, the muscle was excised, weighed, and fixed in Bouin’s fixative. The muscles were embedded in Paraplast (Monoject Scientific, St. Louis), sectioned at 7 μm, and stained with hematoxylin and eosin for histological examination. Samples from the proximal, middle, and distal portions of the muscles were examined for the histological pattern of regeneration.

**Statistical Analysis**

Results are reported as the mean±SEM diameter change of the arterioles. The mean change in arteriolar diameter for each concentration of norepinephrine and adenosine at 7, 14, and 30 days after grafting was compared by an unpaired t test with the mean change in arteriolar diameter of the same concentration in normal control muscle. A value of p<0.05 was accepted as representing a significant difference.

**Results**

**Vasoreactivity**

Under control conditions in normal muscles, the diameter of the arterioles increased linearly in response to increasing concentrations of adenosine (Figure 2). A suffusate concentration of 10⁻⁴ M adenosine caused an increase of 101±5% (mean±SEM) in the diameter of the control arterioles. The mean increase in diameter was 43±6% at a suffusate concentration of 10⁻⁵ M adenosine and 15±4% at a concentration of 10⁻⁶ M. The diameter of the arteri-
TABLE 1. Response of Arterioles in Control Muscle and of Arterioles in Regenerating Muscle to Norepinephrine

<table>
<thead>
<tr>
<th>Norepinephrine concentration</th>
<th>Days after autografting</th>
<th>Control</th>
<th>7 days</th>
<th>14 days</th>
<th>30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10^{-8}$ M</td>
<td>Decrease (%)</td>
<td>8±1</td>
<td>9±2</td>
<td>5±1</td>
<td>13±3</td>
</tr>
<tr>
<td>$5\times10^{-8}$ M</td>
<td>Decrease (%)</td>
<td>20±2</td>
<td>14±2*</td>
<td>20±2</td>
<td>22±3</td>
</tr>
<tr>
<td>$10^{-7}$ M</td>
<td>Decrease (%)</td>
<td>28±2</td>
<td>16±3*</td>
<td>27±3</td>
<td>29±4</td>
</tr>
</tbody>
</table>

Values are mean±SEM for percent decrease in diameter; n=number of arterioles.

In the vasoreactivity studies, there were significant differences between the diameter of the arterioles studied in 7-day grafts (24.5 μm) and the diameters studied in 14-day grafts (12.4 μm), in 30-day grafts (12.4 μm), and in control arterioles (11.9 μm). Somewhat larger diameter arterioles were studied in 7-day grafts. These 7-day grafts were characterized by large arterioles and venules and by multiple capillaries in a plexiform pattern (Figure 3). There were no other arterioles that could be identified confidently as such. Many of the arterioles and venules had capillary sprouts emanating from them. Third-order transverse arterioles were found consistently only in the 30-day grafts. There was a uniform response of the arterioles to the topically applied vasoactive substance. Even...
unusual appearing vessels, including those with loops, dilated and constricted uniformly (Figure 4).

**Structural and Histological Development**

The structural pattern of revascularization of the regenerating skeletal muscle grafts followed an orderly, rapid progression from a disorganized, plexiform capillary pattern to a highly structured pattern in which the capillaries ran parallel to the muscle fibers, and the feeding arterioles and collecting venules were perpendicular to these capillaries.

The vascular pattern of the 7-day graft was dominated by a disorganized, plexiform capillary network and variable degrees of spontaneous extravasation of the fluorescein-labeled albumin (Figure 3). Multiple large arterioles and venules had highly irregular walls and, at times, a nongeometric branching pattern. Long spiderlike capillaries projecting from larger arterioles and venules were seen in every field. Many fields did not have large arterioles or venules but, rather, were dominated by a plexiform capillary network only. Qualitatively, rapid flow was observed throughout every area of the graft observed.

The vascular pattern of the 14-day grafts showed a capillary pattern that was beginning to assume a parallel structure. The arterioles and venules were characterized by abrupt changes in size and by the presence of multiple large vascular loops (Figures 4 and 5). These loops were found in both arterioles and venules and were associated with circular flow patterns; they were also the sites of origination of multiple fine capillaries. These capillaries were seen emanating only from the areas of the venules in which there were loops. The length of the capillaries between many of the feeding arterioles and collecting venules was very short, and they almost appeared like arteriovenous shunts. White blood cells in venules were frequently seen to be marginated and rolling along the venule walls.

The vascular pattern of the 30-day muscle grafts was characterized by a structured microcirculation in which the capillaries ran parallel to the direction of the muscle fibers and the relation between the feeding arterioles and the venules appeared nearly normal. Vascular loops were rarely seen. The pattern of branching of the arterioles and venules appeared nearly normal. However, there were areas in the grafts in which the arterioles and venules were larger than normal; furthermore, they retained some abnormalities in shape.

Histological sections of these skeletal muscle grafts showed a typical pattern of regeneration and revascularization. The 7-day grafts contained a nonvascularized core of muscle fibers in a persisting state of ischemic necrosis. Surrounding this core was a newly vascularized outer zone that contained a gradient of regenerating muscle fibers, ranging from cross-striated myotubes at the periphery to myoblasts near the inner border of this zone (Figure 6A). The 14-day grafts were composed principally of regenerating muscle fibers. The center of the graft commonly contained small and irregularly oriented muscle fibers, which occupied the last remnants of the former ischemic core (Figure 6B). The 30-day grafts consisted of mature regenerating muscle fibers (Figure 6C). However, central nuclei persisted, and there was significant variation in the cross-sectional areas of these muscle fibers. These grafts contained greater amounts of interstitial connective tissue than did control muscles.

**Discussion**

In this study, we found a strikingly different recovery of responsiveness to adenosine and norepinephrine by regenerating arterioles of the tibialis anterior muscle autografts than that reported for regenerated arterioles within fiber bundles of the EDL muscle grafted ectopically to the hamster cheek pouch. In this study, regenerating arterioles within the tibialis anterior muscle grafts rapidly regained responsive-
ness to norepinephrine and adenosine (by 7 days after grafting). In addition, the response to norepinephrine and adenosine by the regenerated arterioles was similar to control values by 14 days and by 30 days after grafting, respectively (Figure 2 and Table 1). In contrast, regenerated arterioles within the EDL muscle grafted to the hamster cheek pouch were reported not to respond to adenosine until 60 days after grafting nor to norepinephrine until 90 days after grafting.5 Furthermore, by 180 days, the responsiveness to these vasoactive agents remained diminished. Thus, the responsiveness of regenerating arterioles of the in situ autografted tibialis anterior muscle grafts occurs earlier and more completely than that reported for fiber bundles of the EDL muscle grafted ectopically to the hamster cheek pouch.

The differences in the responsiveness of the regenerating arterioles between these studies could be due to methodological differences between the studies, but more likely, it represents a real biological difference. The skeletal muscle grafts in both studies were immersed in bupivacaine to ensure uniform myocyte destruction.7 In addition, the tibialis anterior muscle and the EDL muscle of the hamster have similar fiber composition and thus should have a parallel response to the ischemia of the grafting procedure. The major differences between the two studies were the sites of grafting and the intact, whole structure of the tibialis anterior muscle graft. These differences may have accelerated significantly the rates at which these grafts became revascularized.

Differences between the two sites of grafting include the mechanical forces on the graft and the vascularity of the surrounding tissues. In our study, because the tibialis was grafted back into the hind leg and the tendons were resutured, the muscle grafts underwent regular mechanical stretch during ambulation. In contrast, there was little mechanical stretch on the bundles of EDL muscle grafted onto the cheek pouch. Thoma11 showed that modeling of a vascular system depends largely on mechanical factors, such as the tension exerted on the blood vessels during their development. In addition, immobilization itself can impair significantly the revascularization of injured muscles. Jarvinen12 has shown that, in mobilized muscles, the sprouting of new capillaries occurs more rapidly and intensively than in injured muscles treated by immobilization.

Another difference between the sites of grafting is the vascularity of the surrounding tissue. The hamster cheek pouch consists of a thin mucosaecolar membrane and a single-cell-thick muscle layer, whereas the tibialis anterior is surrounded by well-vascularized skeletal muscle laterally and posteriorly and by the tibia medially. The greater vascularity in

**FIGURE 5.** Image-enhanced photograph showing a venule (177 μm) with an abrupt branching pattern from a 14-day graft. This branch does not appear to be part of the normal geometric pattern of branching of a venule but rather a haphazard connection between two preexisting venules.
the surrounding tissue of the hind leg may have resulted as a higher ambient Po2 surrounded the graft immediately after grafting, thereby reducing ischemic injury at the edges of the graft. In addition, it may have resulted as a more rapid resumption of blood flow to the graft.

The intact, whole structure of the tibialis anterior muscle in which the microcirculation is not disrupted
at the time of grafting may have also been an important factor accounting for the differences between these studies. The initial ingrowth of a vascular network is the most critical early factor in the regeneration of any tissue. Regeneration of a tissue in which the microcirculation is intact at the time of degeneration has been shown to influence the rate of regeneration significantly. One way an intact microcirculation at the time of degeneration may facilitate significantly the rapidity of regeneration is by the availability of preexisting vascular pathways into which new blood vessels can grow. Hansen-Smith et al. using the presence of a loose, redundant basal lamina as an indication of reutilization of a preexisting vascular pathway, found a ratio of new to preused pathways of 10:1 for capillaries and 2:1 for arterioles and venules in regenerating EDL muscle in rats. A significant factor explaining the rapid and early return of function of the arterioles of the tibialis anterior muscle graft may be that the presence of an intact microcirculation of a whole, intact muscle permits a more rapid revascularization of the graft after the initial connections are made with blood vessels surrounding the graft.

Examination of the architecture of the microcirculation on the surface of these grafts (Figures 3 and 4) and the histology of the muscle grafts (Figure 6) revealed a rapid, orderly, and progressive maturation of the microcirculation and the skeletal muscle, which paralleled the return of normal responsiveness of the arterioles. The 7-day grafts were characterized by a plexiform appearance of the microcirculation in which spontaneous extravasation was seen frequently. This rudimentary circulation quickly evolved to form a pattern of multiple vascular loops in which there were short connections between arterioles and venules. Capillaries draining directly into venules occurred at the site of the loop. Capillaries appeared to develop from both the arterioles and venules. In addition, capillary branches were observed on large (>15 μm) arterioles and venules. This origination of capillaries from both arterioles and venules is a different pattern of microvascular development from that reported in other models of angiogenesis, in which capillaries arose only from small venules. By 30 days, the relations between the feeding arterioles and venules appeared normal, the vascular loops resolved, the redundant circulation receded, and the microcirculation returned to the normal pattern for skeletal muscle.

Some of the results as well as the methods used in this study deserve further comment. The explanation for the reduced responsiveness of the regenerated arterioles within the 7-day grafts may not be due to a...
reduced responsiveness but rather to a lower resting tone (resting diameter). This explanation could be suggested by the larger mean resting diameters that were identified in the arterioles studied at that time. One problem with this explanation is that a larger-than-anticipated response to the application of a given dose of norepinephrine might also be expected, but this was not observed. In fact, the response to norepinephrine was diminished rather than accentuated. These larger arterioles were the only ones that could be confidently identified as such. The plexiform network of smaller vessels made distinctions between arteriole, capillary, and venule difficult. These other vessels could not be identified as arterioles because there was no readily definable microvascular unit in 7-day grafts. Thus, we believe it is unlikely that the larger resting mean diameter of the 7-day grafts was a significant factor in their reduced responsiveness to topically applied adenosine and norepinephrine.

Whether the changes in vasoreactivity and pattern of revascularization that we observed on the surface of the tibialis anterior represented that which occurred in the deeper aspects of the muscle cannot be determined in this study. However, in a previous study of light microscopic and ultrastructure changes during skeletal muscle regeneration, it was shown that although the outer core of the muscle showed a “more mature” pattern earlier during the course of regeneration than the deeper muscle, eventually there was uniform regeneration of the microcirculation and skeletal muscle fibers throughout the graft. We documented similar changes during regeneration of the muscles during this study. Thus, although the time course of changes within the regenerated microcirculation will differ at different times after the initiation of regeneration, ultimately the same process occurs uniformly throughout the muscle.

There is a rapidly expanding body of knowledge concerning the effect of light on vascular smooth muscle reactivity. Furchgott and associates have shown that arterial smooth muscle placed in active contraction in a water bath relaxes on exposure to light. This relaxation is reversible and is a hyperbolic function of the radiation intensity. Light-induced vasoreactivity in these studies is potentiated by low temperatures and is least effective at wavelengths >450 nm. Light can also cause vascular smooth muscle constriction in the presence of photosensitizing drugs, such as hematoporphyrins, and free fluorescein. The effects of light on the microcirculation in vivo in studies using fluorescent intravital microscopy have been identified by Damon and Duling. The effects of light in these preparations were unpredictable and consisted of either vasodilatation, vasoconstriction, or the initiation of vasomotion.

In our preliminary studies of the tibialis anterior muscle, the effects of light on the microcirculation were characterized predominantly by persistent vasoconstriction and, at times, the initiation of vasomotion. To minimize the effect of light-induced changes on vascular smooth muscle reactivity, a number of modifications were made in the preparation. First, we found that limiting our exposure of light to <1 minute and preferably <30 seconds reduced the effect of light on the smooth muscle. Second, the use of rhodamine as a fluorescent label was associated with fewer light-induced changes than was fluorescein. In addition to the use of rhodamine, we used two special filters (model KGB12, Leitz) that removed all of the wavelengths <450 nm. This effect of light on the reactivity of the microcirculation was observed very rarely in the regenerated muscle. This lack of effect of the light on reactivity of regenerating arterioles is intriguing and suggests that a mediator of this effect might have been absent in the regenerated microcirculation or that there are differences in the reactivity of the smooth muscle itself.

In conclusion, this study has established a rapid and complete return of responsiveness by regenerating arterioles to adenosine and norepinephrine in a model of regeneration in the hind leg of the hamster, in which the skeletal muscle was structurally intact at the onset of degeneration. Our results, in contrast to previously published work, suggest that the responsiveness of regenerating arterioles returns to normal after regeneration. Perhaps of even greater significance are the questions these results raise about many of the experimental models that are used currently to study regeneration and angiogenesis. These models use bits of tissue that are transplanted to ectopic sites for regeneration. Our results show that the intactness of the microcirculation at the time of initiation of regeneration and the local environment of the tissue may have substantial effects on the nature and extent of regeneration. These effects must be taken in account when interpreting results from such models.

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References

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