

Ectopic fibrogenesis induced by transplantation of adipose-derived progenitor cell suspension immediately after lipoinjection.

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Adipose tissue has its own tissue-specific progenitor cells, a subpopulation of which has been shown to have multipotency and called adipose stem cells or adipose-derived mesenchymal stem cells (1, 2). During a clinical trial in which soft tissue is augmented by transplantation of progenitor-enriched adipose tissue (cell-assisted lipotransfer, or CAL), we have encountered incidence of an unexpected complication: local ectopic subcutaneous fibrogenesis. Patients participating in the trial did so under informed consent approved by individual review boards.

CAL was designed based on the finding that aspirated fat tissue contains many fewer vessels and adipose progenitor cells than intact fat tissue. This may explain the tendency of transplanted aspirated fat to atrophy during the first six months post-transplantation (3). In the relevant clinical trial, the stromal vascular fraction (SVF) comprising 10-40% adipose progenitor cells was freshly isolated from aspirated fat via collagenase digestion and transplanted together with aspirated fat tissue grafts (4).

In 146 cases, SVF cells were used as a cell pellet, mixed with and attached to aspirated fat tissue grafts before injecting into fatty and muscular layers of breast mounds. On the other hand, in 2 cases, SVF cells isolated from 600 ml aspirated fat were separately injected as a cell suspension in 60ml of saline into both breast mounds (30 ml per side) immediately after conventional lipoinjection. Although grafted fat survived well and fibrogenesis in the breasts or surrounding tissues was not seen in the former group, fibrous tissue formation was observed in both cases of the latter group 3 months after treatment. In the two cases, breast mounds were somewhat hard to the touch; inspection by CT scan detected unexpected fibrosis in the subcutaneous fat layers. In the thinner patient of the two (Figure 1), fibrous tissue approximately 10 mm thick had formed on the sternum and caused anterior elevation of the skin, which was treated

with local injections of triamcinolone acetonide at 6 and 8 months. Furthermore, lymphadenopathy was seen at the left abdominal wall and the left inguinal region at 3 months and gradually disappeared by 12 months.

Fibrogenesis results from persistent inflammation, in which tissue remodeling and repair processes are impaired and injured cells are replaced not with cells of the same type but with connective or scar tissue (5). As fibrogenesis was seen only when SVF cells were injected separately as a cell suspension, a non-physiological environment in which adherent adipose progenitors cells are suspended in saline solution may give rise to the unexpected differentiation and migration of the cells. After large-volume lipoinjection, tissue injury, edema, hemorrhage and local inflammation are commonly seen, and transplanted adipose progenitor cells are temporarily placed in and stimulated by an ischemic and inflammatory microenvironment.

These findings provide some insights into a therapeutic strategy for future cell-based therapies involving *adherent* stem/progenitor cells. **Previous experimental studies demonstrated that transplanted bone marrow-derived mesenchymal stem cells differentiated into myofibroblasts and contributed to liver fibrosis after acute or chronic liver injury (6,7). In cell-based therapies using adherent mesenchymal stem cells, the possibility of unfavorable behaviors such as differentiation into myofibroblasts should be taken into account, even if the cells are derived from adult tissue and have not been substantially manipulated. It may be a resolution to adhere adipose-derived adherent stem/ progenitor cells to cells, tissue, extracellular matrix, or biological scaffold before administration to avoid their unexpected behaviors.**

References

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Figure Legend

Figure 1.

CT scan images taken before (Pre) and 3, 6, 12, and 36 months after treatment (3m, 6m, 12m, and 36m).

Normal mammary glands and the thin fatty layers around them are visible before treatment. Substantial fibrosis had occurred, both diffusely in the transplanted fat surviving around the mammary glands and in the subcutaneous layer over the sternum, at 3 months. The fibrotic mass over the sternum was treated twice with local injections of triamcinolone acetonide at 6 and 8 months and dissipated, but diffuse fibrosis in the breasts remains at 36 months.