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学位論文名	Myoblast Sheet Can Prevent the Impairment of Cardiac Diastolic Function and Late Remodeling After Left Ventricular Restoration in Ischemic Cardiomyopathy （筋芽細胞シートは虚血性心筋症に対する左室形成後の拡張機能障害およびリモデリングを抑制し得る）
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論文内容の要旨

〔方法(Methods)〕

Eight-week old male Lewis rats were used and rat myocardial infarction model was established 2 weeks after left anterior descending artery (LAD) ligation. They were divided into 3 groups: sham operation (n=15; Group-Sham), LVR by plicating the infracted area (n=15; Group-LVR) and MS implantation with LVR (n=15; Group-LVR+MS). In Group-LVR and Group-LVR+MS, LVR was done as follow: 3-4 mattress stitches with 7-0 polypropylene sutures were placed just onto the border line between infarcted and intact myocardium, and the infarcted myocardium was excluded. Myoblasts were isolated from the skeletal muscle of the anterior tibialis from 3-week-old male Lewis rats and made into cell sheet using temperature-responsive culture dishes (UpCell®, Cellseed, Tokyo, Japan). In Group-LVR+MS, 5 layers of myoblast sheets were attached directly to the intact myocardium without sutures subsequently to LVR.

〔成績(Results)〕

Two weeks after LAD ligation, severe dilatation of the LV chamber and severe asynergy of the anterior wall were observed in all the rats. After LVR, left ventricular dimension at end-diastole (LVDd) and end-systole (LVDs) significantly decreased and left ventricular ejection fraction (LVEF) significantly increased in Group-LVR and in Group-LVR+MS 3 days after treatment. Serial echocardiographic study revealed significant LV re-dilatation and decrease of ejection fraction 4 weeks after LVR in Group-LVR. MS implantation combined with LVR prevented those later deteriorations of LV function in Group-LVR+MS. Mitral valve E/A ratio showed significant restrictive pattern after LVR. In Group-LVR, the restrictive pattern progressed even further with time. However, addition of the myoblast sheets implantation attenuated the progression of the restrictive pattern. Four weeks after the operation, a hemodynamic assessment using a pressure-volume loop showed significantly preserved diastolic function in Group-LVR+MS; end-diastolic pressure (LVR vs. LVR+MS: 9.0 ± 6.6 vs. 2.0 ± 1.0 mmHg, $p < 0.05$), the time constant of isovolumic relaxation (LVR vs. LVR+MS: 19.8 ± 2.2 vs. 14.4 ± 1.2 msec, $p < 0.05$), and end-diastolic pressure-volume relationship (LVR vs. LVR+MS 42 ± 23 vs.

13 ± 6, p < 0.05). Histological examination revealed cellular hypertrophy and LV fibrosis were significantly less and vascular density was significantly higher in Group-LVR+MS than in the other 2 groups. RT-PCR demonstrated significantly suppressed expression of transforming growth factor-beta, Smad2, and reversion-inducing cysteine-rich protein with Kazal morifs in Group-LVR+MS.

〔総　括(Conclusion)〕

MS implantation decreased cardiac fibrosis by suppressing the pro-fibrotic gene expression, and attenuated the impairment of diastolic function and the late remodeling after LVR. It is suggesting that MS implantation may improve long-term outcome of LVR for ischemic heart disease.

論文審査の結果の要旨

本論文は虚血性心疾患に対する左室形成術に筋芽細胞シート移植を併施することで、左室形成術の問題点である左室拡張機能障害と再リモデリングを抑制し得るどうかを検討したものである。

ラット慢性心筋梗塞モデルに対し梗塞部位を縫縮する左室形成術を行うと、術後一時的に左室径・左室駆出率の改善を認めるものの、術後4週間目には左室径の再拡大と駆出率の低下を来した。一方、左室形成術に筋芽細胞シート移植を併施すると、術後の心機能低下が抑制され、左室拡張機能の改善が示された。筋芽細胞シート併施群では組織学的に血管新生の増加と左室線維化の抑制を認め、組織線維化の因子であるTGF-β、Smad2、RECKの遺伝子発現の抑制を認めた。

ラット心筋梗塞後左室形成術モデルにおいて、筋芽細胞シート移植は組織線維化に関わる遺伝子発現を抑制し組織の線維化を抑制することで拡張機能障害を改善する可能性が示唆された。

本論文は博士（医学）の学位授与に値するものと認める。