THE SIGNIFICANCE OF ACUTE-PHASE SMALL-FOR-SIZE LIVER GRAFT INJURY IN MOBILIZATION OF CIRCULATING EPCs/MDSCs/TREGS AFTER LDLT FOR HCC PATIENTS

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Introduction and Objective: Higher incidence of tumor recurrence is a major obstacle of living donor liver transplantation (LDLT) for the patients with hepatocellular carcinoma (HCC). We have already demonstrated that acute phase small-for-size liver graft injury plays an important role on late phase tumor recurrence and metastases in a serial animal studies. Understanding the molecular mechanism of acute phase small-for-size liver graft injury is essential for development of therapeutic strategy to reduce the likelihood of tumor recurrence after LDLT. In the current clinical study, we aim to investigate the impact of acute-phase small-for-size liver graft injury on mobilization of circulating endothelial progenitor cells (EPCs), myeloid-derived suppressive cells (MDSCs) and regulatory T cells (Tregs) in HCC patients after liver transplantation and to explore the mechanism therein.

Methods: From May 2000 to November 2009, 115 adult HCC recipients were included in the current study. The intragraft microRNA profiles of the grafts greater (Group 1) and less than 60% (Group 2) of standard liver weight (SLW) were characterized by Low Density Array (LDA) analysis. Post-operative circulating EPCs (CD34+CD133+CD45-), MDSCs (CD34+CD13+CD33+) and Tregs (CD3+CD25+FOXP3+) were compared by FACS analysis. Intragraft hepatic stellate cell activation, macrophage infiltration and gene expression of Rac, Pyk2, Egr-1 and VEGF at the early phase after reperfusion were also detected by immunostaining and real-time RT-PCR, respectively. Clinical-pathological data including the incidence of tumor recurrence and metastasis were compared between the two groups. Results: The patients were grouped into Group 1 (>60% SLW, n=37) and Group 2 (<60% SLW, n=78). The numbers of patients beyond Milan criteria [15/37(40.5%) vs 29/49(59.2%), p=0.838] or UCSF criteria [9/37(24.3%) vs 19/60(31.7%), p=0.1] were similar between the two groups. Much more patients in Group 2 developed tumor recurrence and lung metastasis [19/78(24.4%) vs 3/37(8%), p=0.04]. Level of circulating EPCs was significantly higher in Group 2 (Day 3: 0.09% vs 0.002%, p=0.019; Week 4: 0.12% vs 0.033%, p=0.037; Week 8: 0.0585% vs 0.025%, p=0.018; Week 12: 0.055% vs 0.028%, p=0.025). A tendency of larger populations of circulating MDSCs and Tregs was also found in Group 2. Most of the patients with tumor recurrence had hepatic sinusoidal injury at early phase after liver transplantation. Significant activation of hepatic stellate cells was found in Group 2 together with stronger intragraft protein expression of FAK and CAX compared to Group 1. Intragraft mRNA levels of Egr-1, Rhox, FAK and VEGF were also significantly higher in Group 2. microRNA LDA analysis demonstrated that mir-233, mir-141, mir-1308, mir-548 and mir-576 were differentially expressed between the two groups. These miRNAs were predicted to regulate targeting genes linked to graft injury (MAPK, CCL4 and Egr-1), tumor invasiveness (STAT5, CDC2 and EGFR), angiogenesis (VEGF, FLT4 and ANGPTL5), and macrophage infiltration (MIP2). Conclusion: A significantly higher population of postoperative circulating EPCs, which are mobilized by small-for-size graft injury, may lead to a higher incidence of tumor recurrence and metastasis after LDLT. The distinct intragraft miRNA expression profile linked to acute-phase injury and angiogenesis may play a role in the mobilization of circulating EPCs, MDSCs, and Tregs.

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