pigs were euthanized on day 21. Endoscopic surveillance was performed every week to measure the ulcer healing.

Results ADMSCs delivered by the endoscopic submucosal injection led to more efficient healing of NSAID-related gastric ulcer, with a significant wound closure observed by day 7 compared with the control (IDDF2018-ABS-0194 Figure 1. B, C). Ulcers in the ADMSCs group displayed enhanced re-epithelization and angiogenesis, and reduced inflammation on day 7 and 21 (IDDF2018-ABS-0194 Figure 1. D-G). Moreover, few engrafted ADMSCs showed myofibroblast and epithelial cell phenotype *in vivo*, suggesting the stem cell-assisted ulcer healing may not rely on cell differentiation (IDDF2018-ABS-0194 Figure 1. H, I). A further experiment with submucosal injection of MSC-derived secretome revealed that the therapeutic efficacy of NSAID-related gastric ulcer was comparable to stem cell transplantation (IDDF2018-ABS-0194 Figure 2. A, B). Profiling analysis showed significant up-regulation of genes associated with inflammation, granulation and extracellular matrix remodelling (IDDF2018-ABS-0194 Figure 2. C, D). In addition, the Erk1/2-MAPK pathway was activated by injection of ADMSCs or MSC-derived secretome (IDDF2018-ABS-0194 Figure 2. E, F).

Conclusions Our results showed that endoscopic submucosal injection of ADMSCs served as a novel approach to promote healing of NSAID-related gastric ulcer, while the paracrine activity of stem cell played a more important role in this process (IDDF2018-ABS-0194 Figure 2. G).

Basic Hepatology

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THERAPEUTIC BENEFIT OF ADIPOSE-DERIVED STROMAL VASCULAR FRACTION CELL TRANSPLANTATION IN RATS OF ACUTE-ON-CHRONIC LIVER FAILURE

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Background Adipose-derived stromal vascular fraction (SVF) cells, a rich source of primary stem/stromal cells, are promising for administering cell therapy for patients with acute-on-chronic liver failure (ACLF). We evaluated the therapeutic effects of CD34+/CD34- SVF cells in hepatocyte cotransplantation in a rat model of ACLF.

Methods ACLF was induced in Sprague-Dawley rats by temporary bile duct ligation and d-galactosamine administration. Donor hepatocytes and SVF cells (labelled with the PKH26 fluorescent dye) were freshly isolated from Tg(UBC-emGFP) rats and human adipose tissues, respectively. Sorted CD34 +and CD34- SVF cells were separated using a magnetic bead system. Rat hepatocytes and SVF cells (unsorted and sorted) were intraportally transplanted into ACLF rats. The surviving animals were sacrificed at 1 and 2 weeks after transplantation. **Results** ACLF was evidenced by the development of acute coagulopathy and hepatocyte necrosis in fibrotic livers. Compared with the control group, the unsorted group showed less biliary ductular proliferation and fibrosis at 1 week after transplantation. Prominent biliary ductular proliferation and significantly increased fibrosis were observed in the CD34- group than in

the CD34 +group at 1 week. At 2 weeks, the serum level of alkaline phosphatase was significantly lower in the CD34 +group than in the CD34- group. The transplanted SVF cells were found in the periportal regions at 1 week, whereas donor hepatocytes were rarely detected.

Conclusions Compared with CD34- SVF cells, cotransplantation of CD34 +SVF cells resulted in the early amelioration of liver fibrosis and biliary ductular proliferation in ACLF rats.

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GENOMIC HETEROGENEITY AND CLONAL EVOLUTION OF MULTIFOCAL HEPATOCELLULAR CARCINOMA

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Background Hepatocellular carcinoma (HCC) often presents with multiple tumours within the liver. Although recent genomic studies evaluating intratumor heterogeneity, the identification of inpatient heterogeneity (IPH) and its impact on targeted therapy for multifocal HCC remain unclear. We aimed to characterise genomic architecture, infer the clonal evolution of multifocal HCC, and explore whether genomic profiling could help select suitable patients for targeted therapy.

Methods 43 tumour samples from 11 multifocal HCC patients were employed for whole-genome sequencing, whole-exome sequencing and RNA sequencing. Somatic mutations, copy number alterations (CNAs), structural variations (SVs), hepatitis B virus integrations, as well as clonal evolution and drug-gable targets of each tumour were analysed.

Results We identified substantial IPH in mutational profiles, CNAs, SVs and clonal evolution among tumours separated by anatomical locations within the same patient. 41 out of 43 tumour samples in our study belong to intrahepatic metastasis. Phylogenetic analysis found that only 31% of the driver alterations were truncal events, indicating evident IPH and branched tumour evolution of multifocal HCCs. Moreover, only 23% of druggable alterations were mapped to trunks. Of note, sorafenib sensitive targets were identified in the trunk of only one out of five patients.

Conclusions Our study provided a detailed view of IPH and clonal evolution of multifocal HCC. Most tumours in our cohort belong to intrahepatic metastasis and follow the scenario of branched tumour evolution. Majority of druggable targets are non-truncal alterations, emphasising the importance of multiple-tumor-sampling of all foci from multifocal HCC patients for personalised targeted therapies.

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SUPER-ENHANCER-ASSOCIATED MASTER TRANSCRIPTIONAL CIRCUITRY IN NAFLD-HCC DEVELOPMENT

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