**Supplemental Material**

**Supplementary Table S1.** Antibodies and antibody dilution used for immunohistochemical analyses.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Antibody** | **Company** | **Clone** | **Species** | **Dilution** |
| Ki-67 | GeneTex | SP6 | Rabbit | 1:100 |
| CD31 | Abcam | Polyclonal | Rabbit | 1:75 |
| CD3 | DCS | SP7 | Rabbit | 1:100 |
| CD45RA | Serotec | OX-33 | Mouse | 1:75 |
| CD163 | Serotec | ED2 | Mouse | 1:500 |
| Act. Caspase-3 | Cell Signaling | Polyclonal | Rabbit | 1:200 |
| Hep Par-1 | DAKO | OCH1E5 | Mouse | 1:50 |

**Supplementary Table S2.** Characterization of human HCC.

|  |  |  |
| --- | --- | --- |
| **No.** | **Tumor size (cm)** | **Grading** |
| 1 | 4.5 | G3 |
| 2 | 4.2 | G3 |
| 3 | 7 | G2 |
| 4 | 10 | G2 |
| 5 | 9 | G3 |
| 6 | 11.5 | G3 |
| 7 | 2.5 | G3 |

**Supplementary Table S3.** Number of tumors per analyzed animal of DEN and McA model.

|  |  |
| --- | --- |
| **DEN** | **McA** |
| rat ID | # | rat ID | # |
| 744 | 6 | 803 | 3 |
| 745 | 6 | 804 | 17 |
| 746 | 5 | 805 | 8 |
| 747 | 5 | 806 | 5 |
|  |  | 807 | 14 |
|  |  | 809 | 13 |

**Supplementary Fig. S1. Schematic of study design**. (A) Orthotopic HCC was induced by 8 weeks of oral DEN feeding (top) or by portal vein infusion of McA-RH 7777 cells (bottom). Animals were imaged weekly (DEN) or every 4 days (McA) by multiparametric MRI as indicated (black arrows) and received PET scans (asterisk) before euthanasia. (B) Sorafenib treatment was administered in tumor bearing animals for 14 (DEN) or 7 (McA) days and multiparametric MRI was applied on days -1, 0, 1, 7 and 14, respectively (black arrows).

**Supplementary Fig. S2. Macrophage and T-lymphocyte infiltration in DEN and McA animals.** (A) Significantly increased intralobular infiltration by CD163+ macrophages is detected in DEN fed animals. Few intratumoral macrophages are identified in both models. (B) Significantly increased infiltration by CD3+ T-lymphcytes is seen intratumorally in DEN induced and peritumorally in McA tumors.

**Supplementary Fig. S3. aCGH analyses.** (A) Principal component analysis (PCA) of aCGH data revealed that chromosomal aberration patterns are more similar within the group of McA tumours compared to the DEN induced HCCs. (B-E) Synteny analysis of genomic copy number alterations identified in the DEN untreated (B), DEN treated (C), McA untreated (D) and McA treated (E) rats (right halfs of circles) with genomic copy number profiles from cryptogenic 13 HCCs (left halfs of circles). Proportions of copy number gains in the rat model and human data group, respectively, are indicated by blue bars and copy losses by red bars. Copy number regions detected in the rat model are connected to the appropriate syntenic regions of the human genome by randomly colored lines.

**Supplementary Fig. S4. Tumor vascularization and necrosis in human HCC.** (A)Semiquantitative analysis ofvessel lumen area in human HCC reveals a larger vessel lumen area than in McA tumors. (B) Semiquantitative analysis of the relative necrosis area in human tumors reveals less necrosis compared to McA tumors. Mean ± SEM and *p* values are displayed. (C) Representative photomicrograph and mask of CD34 antibody staining. Scale bar 100 µm.