Sorafenib perpetuates cellular anticancer effector functions by modulating the crosstalk between macrophages and natural killer cells.

Alternatively polarized macrophages (M?) shape the microenvironment of hepatocellular carcinoma (HCC) and temper anticancer immune responses. We investigated if sorafenib alters the HCC microenvironment by restoring classical macrophage polarization and triggering tumor-directed natural killer (NK) cell responses. In vivo experiments were conducted with sorafenib (25 mg/kg)-treated C57BL/6 wildtype as well as hepatitis B virus (HBV) and lymphotoxin transgenic mice with and without HCC. Monocyte-derived M? or tumor-associated macrophages (TAM) isolated from HCC tissue were treated with sorafenib (0.07-5.0 µg/mL) and cocultured with autologous NK cells. M? and NK cell activation was analyzed by flow cytometry and killing assays, respectively. Cytokine and growth factor release was measured by enzyme-linked immunosorbent assay. Short-term administration of sorafenib triggered activation of hepatic NK cells in wildtype and tumor-bearing mice. In vitro, sorafenib sensitized M? to lipopolysaccharide, reverted alternative M? polarization and enhanced IL12 secretion (P = 0.0133). NK cells activated by sorafenib-treated M? showed increased degranulation (15.3 ± 0.2% versus 32.0 ± 0.9%, P< 0.0001) and interferon-gamma (IFN-?) secretion
(2.1 ± 0.2% versus 8.0 ± 0.2%, P< 0.0001) upon target cell contact. Sorafenib-triggered NK cell activation was verified by coculture experiments using TAM. Sorafenib-treated M? increased cytolytic NK cell function against K562, Raji, and HepG2 target cells in a dose-dependent manner. Neutralization of interleukin (IL)12 or IL18 as well as inhibition of the nuclear factor kappa B (NF-κB) pathway reversed NK cell activation in M?/NK cocultures. Conclusion: Sorafenib triggers proinflammatory activity of TAM and subsequently induces antitumor NK cell responses in a cytokine- and NF-κB-dependent fashion. This observation is relevant for HCC therapy, as sorafenib is a compound in clinical use that reverts alternative polarization of TAM in HCC. (HEPATOTOLOGY 2013; 57:2358-2368).