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Cell-selective delivery of interferon gamma peptidomimetic inhibits chronic liver fibrosis and tumor angiogenesis *in-vivo*

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Till date, no pharmacotherapy is available for liver fibrosis. Activated hepatic stellate cells or myofibroblasts are the key extracellular matrix producing effector cells. Thus, pharmacological inhibition of these cells might lead to an effective therapeutic therapy for liver fibrosis. Interferon gamma (IFNγ) is highly potent anti-fibrotic cytokine but it failed in clinical trials due to reduced efficacy and severe adverse effects. Here, we employed an IFNγ peptidomimetic (mimIFNγ) that lacks the extracellular receptor recognition sequence but retains the agonistic activities of IFNγ. Since, platelet-derived growth factor receptor beta (PDGFβR) expression is highly over-expressed on key pathogenic cells, we conjugated mimIFNγ to a bicyclic PDGFβR-binding peptide (BiPPB) for selective delivery. The synthesized targeted IFNγ peptidomimetic (mimγ-BiPPB) was extensively investigated for anti-fibrotic and adverse effects in acute or chronic CCl4-induced liver fibrosis mouse models. Furthermore, the construct was investigated for anti-angiogenic and anti-tumor effects in C26-colon carcinoma mouse model. The targeted mimγ-BiPPB construct markedly inhibited early and established hepatic fibrosis in mice. Native IFNγ induced only moderate reduction in fibrosis, while untargeted mimIFNγ and BiPPB had no effect. In addition, untargeted IFNγ significantly induced systemic inflammation and MHC-II expression in brain while mimγ-BiPPB did not induce off-target effects. Furthermore, in C26-colon carcinoma tumor-bearing mice, mimg-BiPPB exhibited significant reduction in tumor angiogenesis and size, whereas other treatments showed no effect. The present study demonstrates the beneficial effects of cell-specific targeting of IFNγ peptidomimetic to the disease-inducing cells and therefore represents a highly potential therapeutic approach to treat chronic diseases.

Biography

Ruchi Bansal has completed her PhD (funded by Ubbo Emmius International fellowship) in 2012 from University of Groningen, The Netherlands. In 2011, she received EASL Sheila Sherlock research fellowship (European Association for the Study of the Liver), and The Ruth and Richard Julin's Foundation Swedish research grant for her Post-doctoral research at Karolinska Institute. In 2014, she received prestigious VENI Innovation grant (ZonMw, The Netherlands Organisation for Scientific Research (NWO)) to pursue liver-targeted research in MIRA Institute, University of Twente, The Netherlands. She has published more than 15 papers in highly reputed journals and received several young investigator awards.

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