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4-methylumbelliferone-mediated polarization of M1 macrophages correlate with decreased hepatocellular carcinoma aggressiveness in mice

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Abstract

Hepatocellular carcinoma (HCC) arises in the setting of advanced liver fibrosis, a dynamic and complex inflammatory disease. The tumor microenvironment (TME) is a mixture of cellular components including cancer cells, cancer stem cells (CSCs), tumor-associated macrophages (TAM), and dendritic

cells (DCs), which might drive to tumor progression and resistance to therapies. In this work, we study the effects of 4-methylumbelliferone (4Mu) on TME and how this change could be exploited to promote a potent immune response against HCC. First, we observed that 4Mu therapy induced a switch of hepatic macrophages (M ϕ) towards an M1 type profile, and HCC cells (Hepa129 cells) exposed to conditioned medium (CM) derived from M ϕ treated with 4Mu showed reduced expression of several CSCs markers and aggressiveness. HCC cells incubated with CM derived from M ϕ treated with 4Mu grew in immunosuppressed mice while presented delayed tumor progression in immunocompetent mice. HCC cells treated with 4Mu were more susceptible to phagocytosis by DCs, and when DCs were pulsed with HCC cells previously treated with 4Mu displayed a potent antitumoral effect in therapeutic vaccination protocols. In conclusion, 4Mu has the ability to modulate TME into a less hostile milieu and to potentiate immunotherapeutic strategies against HCC.

Figures

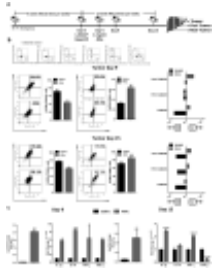


Figure 1 In vivo modulation of hepatic...

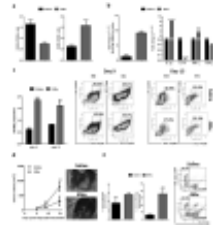


Figure 2 Type 1 macrophages phenotype was...

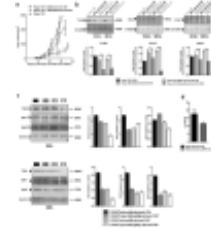


Figure 3 M1 type macrophages induced by...

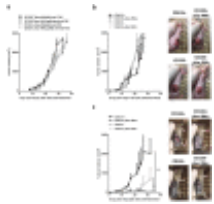


Figure 4 4Mu and M1 hepatic macrophages...

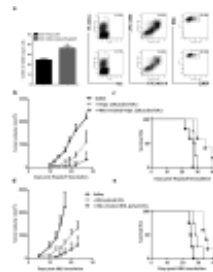


Figure 5 4Mu preconditioning of HCC cells...

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