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Vascular-targeted TNFα and IFNγ inhibited orthotopic colorectal tumor growth

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Tumor necrosis factor alpha (TNFα) and interferon gamma (IFNγ) were originally identified to show potent anti-tumor activity and immunomodulatory capability. Unfortunately, several clinical studies of relevant cancer therapy did not observe significant response in maximum tolerated dose whether given alone or in combination. This unfavorable outcome was largely due to the nonspecific action and widespread systemic toxicity found in the body. We used a phage display technology to identify a tumor vasculature homing peptide (TCP-1) which targeted mainly at the vasculature of colorectal tumors but not normal blood vessels in animals and humans. With this discovery, we biologically conjugated the two immunomodulators individually with TCP-1 in order to provide a targeted therapy and perhaps also lessen the systemic side effects incurred by TNFα and IFNγ when given alone or combined treatment. In this study, we determined the antitumor effect and systemic toxicity of the new conjugates TCP-1/TNFα and TCP-1/IFNγ either given alone or in combination in an orthotopic colorectal tumor model in mice. Targeted delivery of TNFα or IFNγ by TCP-1 peptide exhibited better antitumor activity than unconjugated moieties by inducing more tumor apoptosis and also enhancing antitumor immunity shown by increased infiltration of T lymphocytes inside the tumor. TCP-1/TNFα also normalized tumor blood vessels and increased anti-cancer drug concentration in the tumor. Interestingly combined therapy with TCP-1/TNFα and TCP-1/IFNγ synergistically suppressed tumor growth and alleviated systemic toxicities associated with untargeted therapy. This combination of drug treatment induced massive apoptosis/secondary necrosis in tumors. Taken together, our data demonstrates TCP-1 is an efficient drug carrier for targeted therapy of colorectal cancer (CRC). TCP-1/TNFα combined with TCP-1/IFNγ is a promising combination of immunotherapy for CRC.

Biography

Chi Hin Cho is a Gastrointestinal (GI) Pharmacologist. Currently, he is the Research and Emeritus Professor in the Chinese University of Hong Kong, Hong Kong, China. He has the passion to unveil the various environmental risk factors including alcohol drinking, cigarette smoking and *Helicobacter pylori* infection in the pathogenesis of different disorders in the GI tract, in order to define the different effective therapeutic options in the treatment of GI diseases. Lately, he moves toward more translational research, in particular using small peptides as probes linking up with different anti-cancer agents, targeting tumor vasculature and macrophages for stomach and colon cancer therapies. His working experiences in the hospital and universities as an Administrator and Teacher and also his research accomplishments in inflammation and cancer in the GI tract have made him one of the icons in the field for over 40 years.

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