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Cooperative induction of intestinal stem cells by R-spondin 1 and Slit2 augments chemoradioprotection

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Abstract

How to reduce lethal tissue damage caused by intensive chemoradiotherapy for treating metastatic cancers remains an enigma. Here we tested whether induction of tissue-specific stem cells repairs chemoradiation-induced tissue injury and prolongs overall survival. We found that intestinal stem cells (ISCs) expressed Roundabout 1 (Robo1). R-spondin 1 (Rspo1; a Wnt agonist) and Slit2 (a guidance cue) bound distinctively to the extracellular domains of Robo1, whereas the cytoplasmic CC3 motif of Robo1 bound to LRP6 and promoted LRP6 phosphorylation and association with LGR5, leading to synergistic activation of canonical Wnt signaling and cooperative induction of ISCs for intestinal regeneration. During lethal dosages of chemoradiation, administering a short pulse of Rspo1 plus Slit2 reduced ISC loss, mitigated intestinal impairment and protected animals from death, without concomitantly decreasing tumor sensitivity to chemotherapy. Thus, Rspo1 and Slit2 may serve as therapeutic adjuvants to increase host tolerance to chemoradiotherapy by inducing ISCs.

Biography

Jian-Guo Geng has completed his M.D. and Ph.D. at the age of 33 years from Shanghai Medical University in Shanghai, China, and postdoctoral studies from the University of Oklahoma School of Medicine. He is an associate professor in University of Michigan School of Dentistry. He has published more than 70 papers in reputed journals and serving as an editorial board member of three scientific journals.