DOCTORAL THESIS

Therapeutic potential of a Wnt modulator ICG-001 on nasopharyngeal carcinoma

Chan, Lai Sheung

Date of Award:
2017

ABSTRACT

According to the cancer stem cells (CSCs) hypothesis, CSCs are responsible for the treatment failures. CSCs are a subset of cells possessing stemness properties within the heterogeneous tumor mass. Therapeutic intervention on Wnt signaling is of our great interest because an aberrant Wnt signaling is an important driver to maintain the potency of CSCs. In nasopharyngeal carcinoma (NPC), deregulated expression of the Wnt signaling components is frequently observed. ICG-001 is a selective Wnt modulator (CBP antagonist) that specifically interrupts the interaction between β-catenin and CBP, thereby encourages the interaction between β-catenin and p300 and the subsequent differentiation and reduction of the CSCs subset. For this reason, the present study aimed to evaluate the therapeutic potential of ICG-001 in NPC.

Results showed that ICG-001 inhibited both the migration of the NPC cells and the formation of tumor spheres. In the first part of the mechanistic studies (Chapter 3), ICG-001 was found to restore the expression of miR-150 in NPC cells. MiR-150 was further found to directly reduce CD44 expression and inhibit NPC cell migration. In the second part of the mechanistic studies (Chapter 4), ICG-001 was found to reduce the expression of Evi1 in NPC cells. The effect was accompanied with the inhibition of both the NPC cells migration and the tumor spheres formation. Two molecular axes, namely miR-96/Evi1/miR-449a and survivin/Evi1/miR-449a, were found to be involved in the inhibition of the tumor cell migration and spheroids formation. The therapeutic potential of using this CBP antagonist (ICG-001) in NPC, namely the *in vitro* and *in vivo* efficacy of ICG-001 combined with cisplatin, was examined (Chapter 5). Concurrent treatment of ICG-001 and cisplatin exhibited a synergistic inhibition on the *in vitro* growth and the tumor sphere forming capacity of NPC cells as well as the growth of NPC xenografts. Taken together, results presented in this thesis suggested that ICG-001 (PRI-724 is the analog of ICG-001 currently used in clinical trials) has a therapeutic potential in NPC.

TABLE OF CONTENTS