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APRIL depletion induces cell cycle arrest and apoptosis through blocking TGF-β1/ERK signaling pathway in human colorectal cancer cells

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Abstract It is well documented that a proliferation-inducing ligand (APRIL), a newly found member of tumor necrosis factor superfamily, overexpressed in the majority of malignancies, plays a potential role in the occurrence and development of these tumors. Herein, we demonstrated that APRIL depletion by using RNA interference in human colorectal cancer (CRC) COLO 205 and SW480 cells resulted in cell proliferation inhibition and evoked cell cycle arrest in G0/G1 phase and apoptosis, coupled with decrease in CDK2, Cyclin D1, Bcl-2 expression and an increase of p21 and Bax expression. In addition, the decreased expression of transforming growth factor-β1 (TGF-β1) and p-ERK was also showed in siRNA-APRIL transfected COLO 205 and SW480 cells, whereas the protein expression levels of Smad2/3, p-Smad2/3, and ERK were not significantly changed. Taken together, our results indicate that APRIL depletion induces cell cycle arrest and apoptosis partly through blocking noncanonical TGF-β1/ERK, rather than canonical TGF-β1/Smad2/3, signaling pathway in CRC cells. Moreover, our study highlights APRIL as a potential molecular target for the therapy of CRC.

Keywords APRIL · Colorectal carcinoma · RNA interference · Cell cycle · Apoptosis · TGF-β1

Introduction

Colorectal cancer (CRC) is one of the most prevalent and deadly cancers in the world. Despite surgical resection and advances in radiotherapy and chemotherapy, long-term survival rates remain extremely poor over the past years. It has been established that CRC arises as a consequence of the accumulation of multiple genetic alterations involving critical genes that control cell proliferation and survival [1, 2]. Therefore, a better understanding of oncogenic signaling mechanism underlying CRC and the identification of new therapeutic targets for treatment of this disease are urgently needed.

A proliferation-inducing ligand (APRIL), also known as TALL-2 and TNFSF13, is a recently found new member of tumor necrosis factor (TNF) superfamily and was named according to its ability to drive tumor cell growth [3, 4]. The gene encoding APRIL is located on human chromosome 17p13, it contains six exons transcribed as three alternatively spliced mRNA of 1.8, 2.1, and 2.4 kb, but it encodes a common 250-amino acid protein. APRIL expression is low in various normal cells, such as monocytes, dendritic cells, T cells, etc. However, studies have confirmed that it is overexpressed in many tumor tissues and many tumor cell lines, especially in the digestive system carcinomas, such as colon carcinoma, pancreatic cancer, gastric cancer, hepatoma and esophageal carcinoma, which suggest that APRIL plays an important role in the occurrence and development of these tumors [5–7].

Feng Wang and Lin Chen have contributed equally to this study.

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