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EDITORIAL

DCLK1 as a Promising Marker for Radioresistance in Colorectal Cancer

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Colorectal cancer (CRC) is considered third in terms of frequency and second regarding of mortality, where it has been estimated, over 1.8 million new colorectal cancer cases and 881,000 deaths occurred in 2018 [1]. It has been accepted that radiation therapy (RT) is a highly efficient method of cancer therapy by which DNA damage in tumor cells inhibits their capacity to divide and proliferate more [2]. Nevertheless, in spite of available new therapeutic techniques, a high number of patients still suffer relapse, largely as a result of intrinsic resistance of tumor cells to radiation. Hence, it is crucial to elucidate the causative mechanism(s) and develop new therapeutic strategies to improve the radiosensitivity of CRC cells [3]. Accordingly, novel therapeutic radiosensitizers are urgently needed for overcoming tumor radioresistance and thus improving the outcome of radiotherapy [4].

Doublecortin-like kinase 1 (DCLK1) is a microtubule-associated protein kinase where marks pancreatic and intestinal stem cells. DCLK1 as an important prognostic marker is involved in normal nervous system development and overexpressed in numerous cancers such as the colon, pancreas, kidney, liver, and esophagus [5]. Cumulative evidence proofs that DCLK1 expression plays a critical role in controlling of several key oncogenes (e.g., c-MYC, KRAS, NOTCH, NFKB, and WNT) involving in cancer stem cells, metastasis, EMT, and cancer cell growth/self-renewal [6, 7]. This provides a basis for DCLK1 as a key regulator for initiation and progression of solid tumors as well as its correlation with chemo-/radiotherapy resistance [8–10].

A number of studies suggested that inhibition of DCLK1 results in suppression and sensitization of tumor cells to radio- and chemotherapy [10–12]. In $Apc^{Min/+}$ mice model, siRNA-mediated knockdown of DCLK1, caused in tumor growth arrest, regression of intestinal polyps and downregulation of pluripotency factors and EMT-associated transcriptional factors of intestinal epithelial cells [13]. Study by Chandracesan et al. (2016) showed that DCLK1 expression in tuft cells via paracrine mechanisms and activation of ATM-mediated DNA-damage response (DDR) promoted intestinal epithelial radio-resistance and self-renewal/survival. On the other hand, loss of DCLK1 expression in tuft cells led to an increase in crypt apoptosis and reduction in pluripotency factors, ATM, gamma-H2AX, and other adaptors in HR repair, after exposure to radiation [11]. In addition, Ji et al. (2018) revealed that miR-15b by targeting DCLK1 not only repress self-renewal and tumorigenicity of CRC, but also improves sensitivity of cancer cells to chemo/radiotherapy [8]. Recently, it was shown that Niclosamide (an FDA-approved anthelmintic drug) prevents lymphoid enhancer-binding factor 1 (LEF1)-mediated transcription of DCLK1 and this led to attenuate cancer stemness and sensitizes CRC to chemoradiation [14]. Taken together, it seems that inhibition of DCLK1 restores the radiosensitivity of cancer cells and provides a novel target for the treatment of CRC. Nevertheless, the molecular mechanism by which silencing DCLK1 mediates the radiosensitivity in colorectal cancer is not elucidated well.

In conclusion, we hypothesized that DCLK1 nhibition could serve as a candidate therapeutic target to reverse radioresistance in CRC,thus, if the results confirm our hypothesis, DCLK1 might be a promising therapeutic target to improve the response of CRC to radiation therapy.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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