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EDITORIAL

Targeting the SPHK1/HIF1 Pathway to Inhibit Colorectal Cancer Stem Cells Niche

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Colorectal cancer (CRC) is one of the most common malignancies worldwide and is one of the major leading causes of death [1]. Many therapeutic methods have been used against colorectal cancer, e.g., chemotherapy (such as 5FU, oxaliplatin, leucovorin), and radiotherapy [2, 3], but despite therapeutic advances, drug resistance and metastases still occur in a high proportion of patients and the treatment process fails [4]. Several factors cause resistance in cancer cells, such as drug inactivation, drug target alteration, drug efflux, DNA damage repair, cell death inhibition, and the epithelial–mesenchymal transition or any combination of these mechanisms [5]. Recently, a small sub-population of tumor cells, termed cancer stem cells (CSCs), with infinite self-renewal potential and the capacity to differentiate into the diverse populations of cells that comprise a tumor, has caught the attention of researchers. They represent the root of cancer that must be eradicated in order to cure it [6]. Increasing evidence indicates that CSCs contribute to drug resistance because the intrinsic characteristics of CSCs include DNA repair capability and regulation of the survival pathway and its extrinsic characteristics or niche microenvironment include hypoxic conditions [7, 8]. Furthermore, many of the normal stem cell pathways such as the Hedgehog (Hh), Notch, and Wnt signaling pathways, which guide cellular proliferation, differentiation, and apoptosis, are also prominent in CSCs [9] while the hypoxia pathway is specific to CSCs and niche. Hypoxia occurs in growing tumors or when access to O_2 in blood vessels is limited, and the hypoxia pathway guarantees the survival of the tumor. The hypoxia pathway is involved in angiogenesis, metastasis, invasion, and drug resistance [10]. Hypoxia-inducible factor (HIF-1α), a key transcriptional factor that plays a critical role in hypoxia-related signaling pathway, increases the expression of cell survival or anti-apoptotic genes such as Bcl-XL and decreases the expression of decoy receptors or pro-apoptotic genes such as DcR2 [11]. Hypoxia is an important pathway in CSCs and especially in niche, if hypoxia pathway is inhibited, the foundation of the life of cancer stem cells such as the survival and metastases and chemoresistance of cancer cells, will be insecure [12]. On the other hand, hypoxia pathway is under the control of Sphingosine kinase 1 or SPHK1 [13]. SPHK1 acts as a lipid kinase that phosphorylates sphingosine to sphingosine-1-phosphate (S1P) which is a new target in cancer therapy [14]. SPHK1 is capable of upregulating PI3K/mTOR/AKT pathway that causes cell survival and cell proliferation and it can also activates AKT and GSK3β then inactivates von Hippel-Lindau tumor suppressor protein (pVHL)-mediated ubiquitin proteasome machinery that a role in degredation of HIF-1α (Fig. 1)[15].

High SPHK1 expression in CRC cell lines and tissue samples has been reported. Also, the key role of SPHK1 in tumor development and progression and its significant association with invasion and metastasis were confirmed [16]. So its role in CSC niche might be important. We hypothesize that if SPHK1 is knocked out in CSC niche as the microenvironment of CSCs, it could increase the response and the effect of chemotherapy with 5fu in CRC patients. Thus, SPHK1 knock out-based chemotherapies may represent a novel approach in CRC cell growth inhibition in early stages.

Conclusion

Chemotherapy resistant is a complex phenomenon that occurs in most cancers. No study to date has examined the effect of inhibition of SPHK1 with the targeting of hypoxia pathway in CSC niche in CRC to improve chemotherapy response. Thus,

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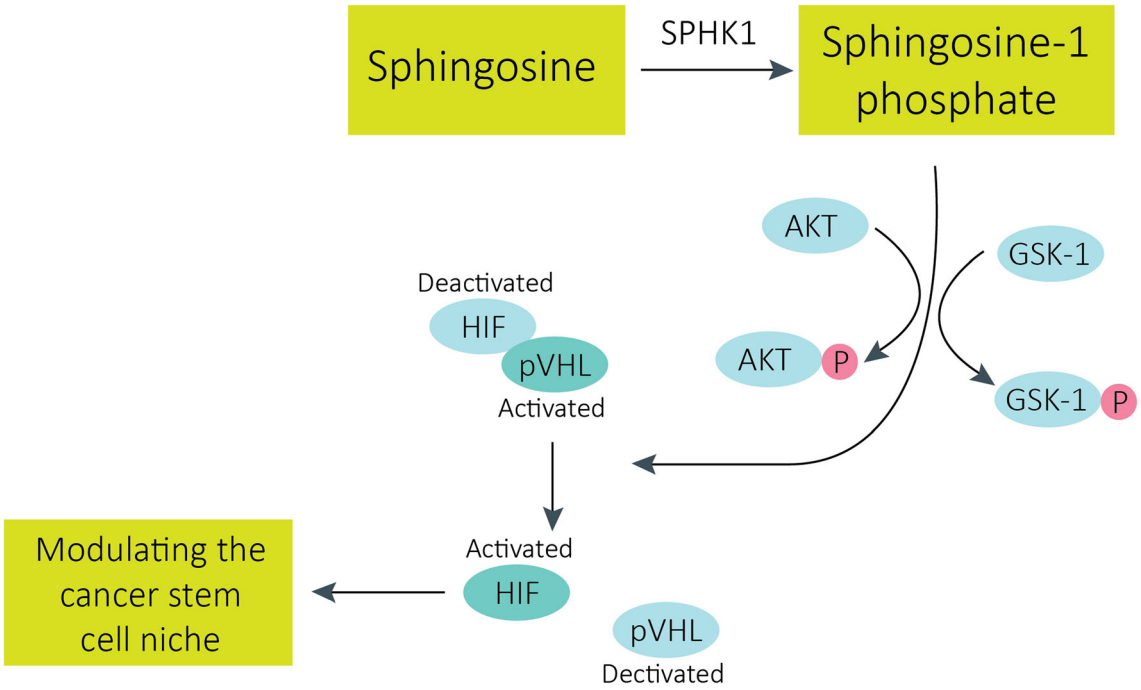

Fig. 1 SphK1 signaling pathway has been reported to modulate the expression of the important genes in cellular proliferation in CSC niche

if the results confirm our hypothesis, the SPHK1-mediated inhibition of HIF-1 to target the hypoxia pathway in CSC niche increases the effects of chemotherapy with 5-fu in CRC patients in early stages.

Compliance with Ethical Standards

Conflicts of Interest The authors have no conflicts of interest to declare.

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