Effects of genetically engineered human neural stem cells expressing cytokine deaminase and interferon-beta on the growth of lymph node metastatic colorectal adenocarcinoma

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ABSTRACT

Genetically engineered stem cells may be advantageous for gene therapy against various human cancers due to their inherent tumor-tropic properties. In this study, we employed human neural stem cells (HBF1.CD, hNSCs) transduced with genes expressing Escherichia coli cytokine deaminase (HBF1.CD) and human interferon-beta (HBF1.CD.IFN-β) as a treatment strategy for human colorectal cancer. CD can convert the prodrug 5-ﬂuorouracil (5-FU) to its active chemotherapeutic form, 5-fluorouracil (5-FU), which induces a tumor-killing effect through DNA synthesis inhibition. IFN-β also strongly inhibits tumor growth by inducing apoptotic process. In RT-PCR analysis, we conﬁrmed that HBF1.CD cells expressed CD gene and HBF1.CD.IFN-β cells expressed both CD and IFN-β genes. A modiﬁed transwell migration assay showed that HBF1.CD and HBF1.CD.IFN-β cells selectively migrated toward SW-620 human colorectal cancer cells. When co-cultured with HBF1.CD or HBF1.CD.IFN-β cells in the presence of 5-FU, the viability of SW-620 cells were signiﬁcantly reduced. The tumor inhibitory effect was greater with HBF1.CD.IFN-β cells, indicating an additional effect of IFN-β to 5-FU. In addition, the tumor-tropic properties of these engineered hNSCs were found to be attributed to chemotactic molecules secreted by SW-620 cells, SDF-1, c-kit, pTAR, p-tPA, and CCR2. An in vivo assay, hNSC treatment signiﬁcantly inhibits the growth of colorectal cancer without any virulent effects on the animals. Consequently, the present results represent that engineered hNSCs and prodrug treatment inhibits the growth of human colorectal cancer cells. Therefore, hNSC therapy may be a clinically effective tool for the treatment of human colorectal cancer.

PURPOSE

The present study describes the potential of genetically engineered stem cells (GESTECs) expressing bacterial cytokine deaminase (CD) and human interferon-β (IFN-β) in reducing tumor growth via tumor tropic effect in colorectal cancer animal models. Also, we investigated whether NSCs have a signiﬁcant migrating capacity for selective targeting via chemotactic signaling as well as therapeutic effect.

RESULTS

CONCLUSION

1. In vitro co-culture data showed that engineered neural stem cells expressing CD and/or IFN-β not only reduced the viability of SW-620 but also inhibited tumor growth.

2. In xenograft cancer model, therapeutic stem cells sufﬁciently inhibited tumor growth by up to 50%.

3. In IHC analysis, proliferation marker was signiﬁcantly down-regulated in NSCs treatment group.

REFERENCES

