CDDpress

www.nature.com/cddis

ARTICLE OPEN

Lenvatinib for effectively treating antiangiogenic drug-resistant nasopharyngeal carcinoma

Qi Sun[1,10], Yujie Wang[2,10], Hong Ji[3,10], Xiaoting Sun[1,4,5], Sisi Xie[1,6], Longtian Chen[6], Sen Li[1], Weifan Zeng[1], Ruibo Chen[1], Qi Tang[1], Ji Zuo[1], Likun Hou[7], Kayoko Hosaka[4], Yongtian Lu[2], Ying Liu[8]✉, Ying Ye[9]✉ and Yunlong Yang[1]✉

Nasopharyngeal carcinoma (NPC) clinical trials show that antiangiogenic drugs (AADs) fail to achieve the expected efficacy, and combining AAD with chemoradiotherapy does not show superiority over chemoradiotherapy alone. Accumulating evidence suggests the intrinsic AAD resistance in NPC patients with poorly understood molecular mechanisms. Here, we describe NPC-specific FGF-2 expression-triggered, VEGF-independent angiogenesis as a mechanism of AAD resistance. Angiogenic factors screening between AAD-sensitive cancer type and AAD-resistant NPC showed high FGF-2 expression in NPC in both xenograft models and clinical samples. Mechanistically, the FGF-2-FGFR1-MYC axis drove endothelial cell survival and proliferation as an alternative to VEGF-VEGFR2-MYC signaling. Genetic knockdown of FGF-2 in NPC tumor cells reduced tumor angiogenesis, enhanced AAD sensitivity, and reduced pulmonary metastasis. Moreover, lenvatinib, an FDA recently approved multi-kinase inhibitor targeting both VEGFR2 and FGFR1, effectively inhibits the tumor vasculature, and exhibited robust anti-tumor effects in NPC-bearing nude mice and humanized mice compared with an agent equivalent to bevacizumab. These findings provide mechanistic insights on FGF-2 signaling in the modulation of VEGF pathway activation in the NPC microenvironment and propose an effective NPC-targeted therapy by using a clinically available drug.

Cell Death and Disease (2022)13:724; https://doi.org/10.1038/s41419-022-05171-3

INTRODUCTION

Antiangiogenic drugs (AADs) are routinely used in patients with various types of solid cancer and effectively prolong patient survival. However, the responsiveness to AADs differs among tumor types. Clinically, bevacizumab, a recombinant humanized monoclonal antibody that neutralizes vascular endothelial growth factor-A (VEGF-A, or VEGF), is used in the first-line treatment of metastatic colorectal cancer (CRC) and produced significant survival improvement [1]. However, in certain types of tumors, AADs only produce limited therapeutic benefits or fail to provide any benefits. In 2011, FDA withdrew metastatic breast cancer from the bevacizumab indication list. Furthermore, most patients with pancreatic ductal adenocarcinoma show intrinsic resistance to bevacizumab [2]. Similar to patients with breast cancer or pancreatic cancer, adding bevacizumab to standard chemoradiotherapy did not show obvious superiority in patients with nasopharyngeal carcinoma (NPC) [3]. These clinical results demonstrate the AAD resistance in certain types of cancer, which is one of the major obstacles to current antiangiogenic therapy. In addition, a current impediment to the clinical use of AAD is the lack of reliable biomarkers to predict AAD therapeutic efficacy [4]. Although under intensive study [5], such biomarkers are still not clinically available.

Accounting for 73,000 deaths in 2018, NPC is an epithelial carcinoma with a specific geographical global distribution, with a high prevalence mainly in Southeast Asia [6, 7]. For early-stage NPC and non-metastatic NPC patients, chemoradiotherapy has shown satisfactory efficacy [8]. However, therapeutic options are still limited for metastatic NPC. Although AAD was recognized as an attractive approach to treating patients with NPC, the clinical results with bevacizumab resistance do not support this view [3]. To solve the bevacizumab resistance issue in NPC patients, in-depth mechanistic studies are urgently warranted. Commonly recognized mechanisms of AAD resistance include: (1) angiogenesis triggered by non-targeted growth factors [9]; (2) recruitment or activation of pro-angiogenic host cells [10, 11]; (3) vessel co-option or vessel remodeling [12, 13]; (4) endothelial cell (EC) transition [14]; and (5) metabolic shifts of tumor cells [15]. Of note,

[1]Department of Cellular and Genetic Medicine, School of Basic Medical Sciences, Fudan University, 200032 Shanghai, China. [2]Department of Otolaryngology, Shenzhen Key Laboratory of Nanozymes and Translational Cancer Research, Shenzhen Institute of Translational Medicine, The First Affiliated Hospital of Shenzhen University, Shenzhen Second People's Hospital, 518035 Shenzhen, Guangdong, China. [3]Department of Radiation Oncology, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, Jiangsu, China. [4]Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden. [5]Oujiang Laboratory (Zhejiang Lab for Regenerative Medicine, Vison and Brain Health), School of Pharmaceutical Science, Wenzhou Medical University, Wenzhou, P. R. China. [6]Longyan First Hospital Affiliated to Fujian Medical University, 364000 Longyan, Fujian, China. [7]Department of Pathology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, P. R. China. [8]Institute of Translational Medicine, Shanghai University, 99 Shangda Road, 200444 Shanghai, China. [9]Department of Oral Implantology, Stomatological Hospital and Dental School of Tongji University, Shanghai Engineering Research Center of Tooth Restoration and Regeneration, Shanghai, China. [10]These authors contributed equally: Qi Sun, Yujie Wang, Hong Ji. ✉email: liuchanger1984@163.com; ying.ye@tongji.edu.cn; yunlongyang@fudan.edu.cn

Edited by Professor Gennaro Ciliberto

Received: 16 February 2022 Revised: 30 July 2022 Accepted: 8 August 2022
Published online: 19 August 2022