FBW7

F-box and WD repeat domain-containing 7(FBW7) is a SCF-type E3 ubiquitin ligase targeting a multitude of oncoproteins for degradation. Acting as one of the most important tumor suppressor it is frequently inactivated in various tumors.

It is recently suggested to be involved in atherogenesis. However, whether FBW7 affects cerebrovascular remodeling during intracranial atherosclerotic stenosis (ICAS) remains unknowns.

Shen et al. found that the expression of FBW7 was decreased in mouse brain microvessels from high-fat diet (HFD)-fed atherosclerotic mice. The reduced FBW7 expression was negatively associated with the remodeling of middle cerebral artery (MCA). Specific loss of FBW7 in smooth muscle cells (SMCs) markedly potentiated brain vascular SMC (VSMC) proliferation, migration and subsequent MCA remodeling in atherosclerotic mice. The increase of total reactive oxygen species (ROS) generation and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity in brain microvessels and VSMCs were enhanced after knockout of FBW7, while the mitochondria-derived ROS was unchanged. Analysis of several key subunits of NADPH oxidase revealed that FBW7 deficiency augmented HFD-induced the increase of Nox1 expression, but had no effect on p47phox and p67phox phosphorylation as well as p22phox expression. Both NADPH oxidase specific inhibitor and Nox1 downregulation abrogated the effects of FBW7 deficiency on MCA remodeling. Immunoprecipitation assay identified that FBW7 interacted with Nox1. FBW7 knockout increased Nox1 protein stability by inhibiting ubiquitin-mediated degradation. Collectively, this study demonstrated that SMC-specific deficiency of FBW7 exacerbates ICAS by facilitating Nox1-derived ROS generation, VSMC proliferation and cerebrovascular remodeling [1)].

Lin et al. aimed to evaluate the relationship of FBW7 with glioma pathology and prognosis, and examine its effect in glioma malignancies and temozolomide (TMZ)-based therapy. Clinical tissues and TCGA database analysis revealed FBW7 expression was correlated inversely with glioma histology and positively with patient survival time. Lentivirus transfection- induced FBW7 overexpression significantly suppressed proliferation, invasion and migration of U251 and U373 cells whereas knockdown of FBW7 by targeted shRNA promoted proliferation, invasion and migration of glioma cells. Most importantly, the expression level of FBW7 was found to affect 50% inhibition concentration(IC50) of U251 and the TMZ resistant variant. Combining TMZ with FBW7 overexpression notably increased the cytotoxicity than TMZ treatment alone, which was conversely attenuated by FBW7 knockdown. Moreover, flow cytometry(FC) analysis showed either overexpression of FBW7, TMZ or the combination increased proportion of G2/M arrest and apoptotic rate whereas FBW7 inhibition reduced G2/M arrest and apoptosis in U251 cells. Finally, mechanistic study found FBW7 overexpression downregulated Aurora B, Mcl1 and Notch1 levels in a time-dependent pattern and this expressional suppression was independent of TMZ. These findings collectively demonstrate the critical role of FBW7 as a prognostic factor and a potential target to overcome chemoresistance of glioblastoma [2)].

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Shen Y, Chen X, Chi C, Wang H, Xue J, Su D, Wang H, Li M, Liu B, Dong Q. Smooth muscle cell-specific knockout of FBW7 exacerbates intracranial atherosclerotic stenosis. Neurobiol Dis. 2019 Aug 21:104584. doi: 10.1016/j.nbd.2019.104584. [Epub ahead of print] PubMed PMID: 31445163.
2)
Lin J, Ji A, Qiu G, Feng H, Li J, Li S, Zou Y, Cui Y, Song C, He H, Lu Y. FBW7 is associated with prognosis, inhibits malignancies and enhances temozolomide sensitivity in glioblastoma cells. Cancer Sci. 2018

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