Osteoprotegerin

Osteoprotegerin (OPG), also known as osteoclastogenesis inhibitory factor (OCIF) or tumour necrosis factor receptor superfamily member 11B (TNFRFSF11B), is a cytokine receptor of the tumor necrosis factor (TNF) receptor superfamily encoded by the TNFRSF11B gene.

The Chinese Glioma Genome Atlas (CGGA) and The Cancer Genome Atlas (TCGA) databases with RNA sequencing and corresponding clinical data were dichotomized into training group and testing group. The immune-related differentially expressed genes (DEGs) associated with 1p/19q codeletion were screened using Cox proportional hazards regression analyses. A prognostic gene signature was established using dataset from CGGA and tested in TCGA database. Subsequently, Xu et al. explored the correlation between the prognostic gene signature and immune response. Thirteen immune genes associated with 1p/19q codeletion were used to construct a prognostic signature. The 1-, 3-, 5-year survival rates of the low-risk group were approximately 97%, 89%, and 79%, while those of the high-risk group were 81%, 50% and 34%, respectively, in the training group. The nomogram which comprised age, WHO grade, primary or recurrent types, 1p/19q codeletion status and risk score provided accurate prediction for the survival rate of glioma. DEGs that were highly expressed in the high-risk group clustered with many immune-related pathways. Immune checkpoints including TIM3, PD1, PDL1, CTLA4, TIGIT, MIR155HG, and CD48 were correlated with the risk score. VAV3 and TNFRFSF11B were found to be candidate immune checkpoints associated with prognosis. The 1p/19q codeletion-associated immune signature provides accurate prediction of OS. VAV3 and TNFRFSF11B are novel immune checkpoints [1)].

Obstructive sleep apnea (OSA) was characterized by chronic intermittent hypoxia, which was an independent risk factor for endothelial dysfunction. Circulating TNFRSF11B might play an important role in promoting endothelial cells dysfunction. We explored the role of plasma TNFRSF11B as a potential mechanism of endothelial dysfunction in OSA patients.

METHODS: The study population consisted of 120 patients with varying severity of OSA and 40 control subjects. Plasma TNFRSF11B levels were measured using human Magnetic Luminex assay.

RESULTS: Our data showed that plasma TNFRSF11B levels were significantly higher in patients with OSA. After adjusting confounding factors, plasma TNFRSF11B levels were independently associated with the presence of OSA (Beta:0.434, 95% CI: 664.096 to 1076.247; $P < 0.001$) and plasma TNFRSF11B levels were positively associated with the apnea-hypopnea index (Beta:0.486, 95% CI: 0.007 to 0.017; $P < 0.001$). Furthermore, plasma TNFRSF11B showed higher discriminatory accuracy in predicting the presence of OSA (AUC:0.964).

CONCLUSIONS: Plasma TNFRSF11B levels were significantly associated with the presence of OSA and its severity. TNFRSF11B could be a plasma biomarker with a positive diagnostic value for premature vascular endothelial dysfunction in patients with OSA [2)].

Juvenile Paget's disease (JPD), an ultra-rare, debilitating bone disease due to loss of functional osteoprotegerin (OPG), is caused by recessive mutations in TNFRFSF11B. A genotype-phenotype

correlation spanning from mild to very severe forms is described.

AIM: This study aimed to describe the complexity of the human phenotype of OPG deficiency in more detail and to investigate heterozygous mutation carriers for clinical signs of JPD.

PATIENTS: We investigated 3 children with JPD from families of Turkish, German, and Pakistani descent and 19 family members (14 heterozygous).

RESULTS: A new disease-causing 4 bp-duplication in exon 1 was detected in the German patient, and a microdeletion including TNFRFSF11B in the Pakistani patient. Skeletal abnormalities in all affected children included bowing deformities and fractures, contractures, short stature and skull involvement. Complex malformation of the inner ear and vestibular structures (2 patients) resulted in early deafness. Patients were found to be growth hormone deficient (2), displayed nephrocalcinosis (1), and gross motor (3) and mental (1) retardation. Heterozygous family members displayed low OPG levels (12), elevated bone turnover markers (7), and osteopenia (6). Short stature (1), visual impairment (2), and hearing impairment (1) were also present.

CONCLUSION: Diminished OPG levels cause complex changes affecting multiple organ systems, including pituitary function, in children with JPD and may cause osteopenia in heterozygous family members. Diagnostic and therapeutic measures should aim to address the complex phenotype [3].

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Xu J, Liu F, Li Y, Shen L. A 1p/19q Codeletion-Associated Immune Signature for Predicting Lower Grade Glioma Prognosis [published online ahead of print, 2020 Sep 7]. Cell Mol Neurobiol. 2020;10.1007/s10571-020-00959-3. doi:10.1007/s10571-020-00959-3

2)
Wen WW, Ning Y, Zhang Q, Yang YX, Jia YF, Sun HL, Qin YW, Fang F, Zhang M, Wei YX. TNFRSF11B: A potential plasma biomarker for diagnosis of obstructive sleep apnea. Clin Chim Acta. 2018 Dec 15. pii: S0009-8981(18)30647-8. doi: 10.1016/j.cca.2018.12.017. [Epub ahead of print] PubMed PMID: 30562485.

3)
Grasemann C, Unger N, Hövel M, Arweiler-Harbeck D, Herrmann R, Schündeln MM, Müller O, Schweiger B, Lausch E, Meissner T, Kiewert C, Hauffa BP, Shaw NJ. Loss of Functional Osteoprotegerin: More Than a Skeletal Problem. J Clin Endocrinol Metab. 2017 Jan 1;102(1):210-219. doi: 10.1210/jc.2016-2905. PubMed PMID: 27809640.