Neutrophil gelatinase associated lipocalin

Lipocalin 2 (LCN2), also known as oncogene 24p3 or neutrophil gelatinase-associated lipocalin (NGAL), is a protein that in humans is encoded by the LCN2 gene.

NGAL is involved in innate immunity by sequestrating iron that in turn limits bacterial growth.

It is expressed in neutrophils and in low levels in the kidney, prostate, and epithelia of the respiratory and alimentary tracts. NGAL is used as a biomarker of kidney injury.

High level expression of lipocalin 2 (LCN2) usually indicates poor prognosis in esophageal squamous cell carcinoma (ESCC) and many other cancers. Our previous study showed LCN2 promotes migration and invasion of ESCC cells through a novel positive feedback loop. However, the key transcription activation protein (KTAP) in the loop had not yet been identified. In this study, we first predicted the most probable KTAPs by bioinformatic analysis. We then assessed the transcription regulatory regions in the human LCN2 gene by fusing deletions of its 5'-flanking region to a dual-luciferase reporter. We found that the region -720/-200 containing transcription factor 7-like 2 (TCF7L2) (-273/-209) and early growth response 1 (EGR1) (-710/-616) binding sites is crucial for LCN2 promoter activity. Chromatin immunoprecipitation (ChIP) experiments demonstrated that TCF7L2 and EGR1 bound directly to their binding sites within the LCN2 promoter as KTAPs. Mechanistically, overexpression of TCF7L2 and EGR1 increased endogenous LCN2 expression via the ERK signaling pathway. Treatment with recombinant human LCN2 protein enhanced activation of the ERK pathway to facilitate endogenous LCN2 expression, as well as increase the expression level of TCF7L2 and EGR1. Treatment with the MEK inhibitor U0126 inhibited the activation by TCF7L2 or EGR1 overexpression. Moreover, overexpression of TCF7L2 or EGR1 accelerated the migration and invasion of ESCC cells. A synergistic effect was observed between TCF7L2 and EGR1 in amplifying the induction of LCN2 and enhancing migration and invasion. Taken together, our study indicates that TCF7L2 and EGR1 are the KTAPs of LCN2, within a positive “LCN2 → MEK/ERK → LCN2” path, to promote the migration and invasion of ESCC cells. Based on their clinicopathological significance, LCN2 and its two expression regulators TCF7L2 and ERG1 might be therapeutic targets for ESCC [1)].

A study determined the association between serum NGAL and iron status in chronic kidney disease with anemia. A total of 154 adult chronic kidney disease (CKD) patients were divided into anemia and without anemia groups. The anemia groups were further subdivided into two groups based on the presence or absence of iron deficiency, defined as a transferrin saturation (TSAT) < 20%. The NGAL was measured for all the 154 patients, and the possible relationships with iron status were analyzed. 27.7% patients with TSAT < 20% presented lower hemoglobin, serum iron, serum ferritin, and higher NGAL values than those without iron deficiency. NGAL was inversely correlated with hemoglobin, hematocrit, MCV, MCH, serum iron, and TSAT. NGAL adequately diagnosed the status of iron deficiency among CKD patients by ROC analysis. The optimal NGAL cutoff value able to identify iron deficiency was found to be > 244.8 ng/mL, with 73.01% sensitivity and 68.29% specificity. CKD patients with anemia presented altered NGAL values as this protein is involved in the maintenance of iron balance. Thus, NGAL might be proposed as a new tool for assessing the iron deficiency and in the management of iron therapy for CKD patients [2)].

1)

Zhao Y, Xia Q, Liu Y, Bai W, Yao Y, Ding J, Lin L, Xu Z, Cai Z, Wang S, Li E, Xu H, Wu B, Xu L, Du Z. TCF7L2 and EGR1 synergistic activation of transcription of LCN2 via an ERK1/2-dependent pathway in esophageal squamous cell carcinoma cells. Cell Signal. 2018 Dec 14. pii: S0898-6568(18)30309-7. doi: 10.1016/j.cellsig.2018.12.007. [Epub ahead of print] PubMed PMID: 30557604.

2)

Xiang D, Wang X, Liu P, Pan Y, Zhang Q, Chi X, Jing Y, Duan X, Wei Q, Wang J, Li M, Wang C. Increased NGAL level associated with iron store in chronic kidney disease with anemia. Clin Exp Med. 2018 Jun 16. doi: 10.1007/s10238-018-0507-4. [Epub ahead of print] PubMed PMID: 29909502.