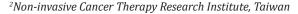


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# Lipocalin 2 could be the Sentinel Marker and Prognostic Factor in Subarachnoid Hemorrhage and Malignant Tumor Progression

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### **ABSTRACT**

Lipocalin 2 (LCN2) is a 25 kDa protein found to be related to inflammatory modulation, cell-cell interaction, and clinical biomarker for acute renal injury. The LCN2 is highly expressed while the metastatic cancer cell invasion occurs and could be detected both in the urine or blood. Under overwhelmed inflammation, the progression of acute renal injury or cerebral ischemia could be aggravated and the serum level of LCN2 increased simultaneously. The neurological deterioration in subarachnoid hemorrhage (SAH) was closely related to neuroinflammation and inadequate microcirculation which might be LCN2 related as well. Here, the authors encourage further investigations to discover the prognostic correlation between LCN2 and SAH.

**Abbreviations:** LCN 2: Lipocalin 2; SAH: Subarachnoid Hemorrhage; DCI: Delayed Cerebral Ischemia; NGAL: Neutrophil Gelatinase Associated Lipocalin; AKI: Acute Kidney Injury; MMP: Matrix Metalloproteinase; BBB: Blood Brain Barrier; SNI: Spared Nerve Injury

# **Mini Review**

Cerebral vasospasm, along with succeeding delayed cerebral ischemia (DCI), are notoriously severe complication subsequent to subarachnoid hemorrhage (SAH). The overwhelmed neuroinflammation plays a crucial role behind while causing a direct brain injury [1]. As injured brain tissue fail to function normally due to deteriorated microcirculation, "vasoconstriction" rather than vasodilation take place with sequential ischemia in a vicious cycle. How to detect the process earlier and give a proper clinical treatment response were always challenging the clinical physician. However, current monitoring methods such as beside transcranial duplex study, computed tomography angiography, or traditional cerebral angiography may require skilled examiner or the exposure to radiation [2]. A reliable biomarker is warranted for monitoring the severity or the progression in SAH. Lipocalin 2 may be a candidate for further study in SAH model. Lipocalin 2 (LCN2), or neutrophil gelatinase associated lipocalin (NGAL), is a 25 kDa protein sharing general structure of lipocalin family with hydrophobic core, which facilitates its binding with lipophilic substances [3].

It was known for its association with inflammatory response in heart [4,5], bowel [6] or even CNS [7]. First purified by Kjeldsen et al. [7] as a 25-kDa protein from neutrophil granules, it was later found by Bundgaard et al. [8] of its large amounts of expression in myeloid cells [8]. Later on, LCN2 plays a crucial role in immunity was hypothesized after the disclosure of the involvement in intercellular iron delivery mechanism [9]. Goetz and his coworkers pointed out that the specificity, along with affinity of LCN2 for bacterial catecholate-type ferric siderophores, which takes part in antibacterial iron-depletion strategy of immune system and explains the phenomena of high serum concentration during inflammation [10]. The hypothesis was proved later in vitro with LCN2 deficient mice with isolated neutrophils showing less bacteriostatic activity [11-13], and in vivo with higher bacterial numbers found in bladders

of LCN2-deficient mice than wild-type mice [14]. This contributes to the prognostic value of acute kidney injury (AKI), which is highly excreted as tubular injury occurs [15,16]. A meta-analysis of data from 19 studies elucidated that urine NGAL levels were found to be diagnostic for AKI [17].

LCN2 covalently binds matrix metalloproteinase-9 (MMP), a gelatinase, or proteolytic enzymes secreted by neutrophils. As a member of superfamily of proteolytic enzymes, MMP-9 is related to disruption of blood brain barrier (BBB) [18]. It was reported that NGAL prevents MMP-9 from degradation [19], and in certain degree contributes to the tumor progression. Independently, LCN2 increases the invasiveness of certain cancer cells, while inhibition of LCN2 expression decreases their invasiveness [20]. In a study designed to examine the difference of LCN2 and MMP-9 expression in the tumor tissues from patients with lung adenocarcinoma, LCN2 expression turned out to be an independent prognostic factor, while expression of MMP-9 failed to indicate overall survival rate difference [21]. More studies showed NGAL/MMP-9 complex seemingly elevates in urine of cancer patients, which may imply the participation of this 125 kDa complex in tumor progression [19,22-24]. However, the physiological and pathological process behind NGAL/MMP-9 complex is still not fully known currently.

Two receptors of LCN2 have been identified, the solute carrier family 22 member 17 (SLC22A17 or 24p3R) and megalin, as the former is located in hippocampus [25], choroid plexus [26], whilst the latter is positioned throughout the brain, expressed by miscellaneous types of cells: neurons, endothelial cells and astrocytes. 24p3R is a cell surface receptor for LCN2 expressed in various organs, which modulates the cellular uptake of LCN2 and diverse physiological processes. Using the spared nerve injury (SNI) model [27], Sangmin et al. found the expression of 24p3R in microglia as well as neurons, while high levels of 24p3R was present in the normal spinal cord. Khizr I et al. suggested the participation of LCN2 in regulating inflammation in the injured spinal cord and 24p3R-expressing spinal neurons is probably sensitive to LCN2. These findings showed that 24p3R, largely expressed in neurons and to some degree in microglia, may modulate the actions of LCN2 under the condition of neuropathic pain. By acting on its receptor, 24p3R, which is spread throughout the spinal cord, LCN2 is virtually involved in the development of pain hypersensitivity [27].

The idea of taking LCN2 as "target cell" gets even stronger when there's a better recovery outcome for spinal injury due to lack of LCN2 [28] and modulation of LCN2 might attenuate Alzheimer's disease [29]. However, there is report that showed seemingly controversial result that LCN2 deficiency had no effect on aggravation of systemic disease [30], supporting the notion of regarding LCN2 as a biomarker, which doesn't have impact on the disease itself while upregulated as disease deteriorates. Hochmeister et al. [31] supported the evidence for regarding LCN2

as biomarker and elucidated that plasma LCN2 level predicts clinical outcome in ischemic stroke model [31]. SAH is a hemorrhagic intracerebral ischemic process and brings catastrophic change to the microenvironment in the brain. The severity of blood brain barrier (BBB) breakdown had high correlation to neuroinflammation and poorer outcome [32], while the hyperpermeability of BBB increase the neutrophils migration toward the brain parenchyma would increase neuroinflammation. LCN2 might be the ideal serum biomarker of SAH disease progression [33] while more clinical studies should be encouraged.

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