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Reviewing biomedical role of Plasma Gelsolin

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Abstract
Gelsolin is circulating in human plasma in extremely high concentrations that is exhausted by intermediaries of inflammation and largely produced by skeletal muscles. Gelsolin is a Ca^{2+} dependant actin-binding and an actin-depolymerizing protein. Owing to capability of gelsolin to swiftly severe F-actin, plasma gelsolin has become a very important injury healing protein in various pathological conditions. Decreased levels of the plasma gelsolin have been reported in human diseases as well as in animal models of diseases. Therefore, pGSN deficiency appears to be a powerful biomarker and a potential therapeutic target in diseases. Here, we review the biomedical functions of gelsolin and impact of gelsolin levels in different disease conditions.

Keywords: Plasma gelsolin, actin severing protein, decrease levels in diseases, physical exercise, prognostic biomarker, gelsolin replacement therapy

1. Introduction
Gelsolin (GSN) is a calcium dependent actin binding protein predominantly responsible in removal of actin filaments released into circulation upon cell injury [1, 2]. The protein is extensively studied and available both intracellularly (cytoplasmic gelsolin, cGSN) as well as secreted protein i.e. plasma gelsolin (pGSN). pGSN is secreted in high amount in skeletal muscles [3] and is present in blood in high levels at ~ 200 ± 50 µg/ml. pGSN levels decrease by 20-50% in several clinical conditions in humans as well as animals.
Scientific literatures have shown that pGSN decline in ICU patients and prognosis of the disease depends upon the rate at which gelsolin levels return to normal or are replenished by exogenous administration of rhuGSN.
There are many reviews in the literature about the structure, activation of gelsolin as well as about the mechanism of action severing by gelsolin and about the relation of gelsolin in health and diseases [4-6]. Therefore, in this review, we will discuss further about the biomedical role of pGSN in various disease conditions affecting humans and in animal models of diseases (Table 1).

2. Acute liver injury
Ito *et al.*, reported a significant decrease in gelsolin concentrations in serial plasma samples obtained from patients suffering from acute liver injury using an Enzyme-Linked Immunosorbent Assay. This decrease in the concentration of gelsolin depends on continuous leakage of actin in response to injury to the liver [7].
Diminished levels of gelsolin were observed in human subjects affected with acute liver injury, myocardial infarction, sepsis and myonecrosis in comparison to the healthy people. The study showed that the prognosis of the disease depends on the extent of reduction in pGSN values, since extra gelsolin is utilized in clearing actin from the circulation [8].

3. Major trauma
pGSN levels can serve as an early prognostic indicator of major trauma. Outcome of patients with rigorous trauma and their stay in the hospital was predicted by evaluating plasma gelsolin concentrations at the time of coming to hospital for treatment. Mounzer *et al.,* 1999 observed that pGSN values were considerably low in patients with severe traumatic injury than the normal human subjects [9].
Extracellular Actin Scavenger System (EASS) has been reported to have role in sequestering the intracellular actin released into circulation upon tissue injury. Similar reports of decline in

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pGSN levels following excessive trauma, burn have also been reported leading to too much reduction of gelsolin in nucleation of actin filaments from the circulation and ultimately lead to multiple organ dysfunction syndromes (MODS) [10, 11]. Plasma gelsolin has been proposed as a prognostic indicator of health status, since there is a direct correlation of pGSN values with outcome of disease as well as gelsolin levels determines the stay of patients in hospital or mortality also [6, 12, 13].

4. Hemodialysis
A decline in pGSN values lead to improper working of kidneys in patients through CKD not on dialysis. These observations concluded that patients with chronic hemodialysis have decreased pGSN and noticeable actin in the circulation, are mainly at risk of mortality [14].

5. Inflammation induced lung injury
In lung injury induced by inflammation due to burn, significant decrease in pGSN values was observed early on

and gelsolin replacement therapy was able to control pulmonary microvascular dysfunction in rats. These findings are in agreement to the theory that plasma gelsolin diminution is responsible for pulmonary microvascular dysfunction during inflammation [15].

In an another study authors observed fall in free gelsolin levels in rats and rabbits in which lung injury was induced oleic acid [16]. In response to injury excessive actin is released in circulation and considerable amounts of gelsolin are depleted due to the creation of circulating actin-gelsolin complexes, which ultimately led to dropped levels of gelsolin.

6. Rheumatoid arthritis
Several studies have reported a decrease in GSN values in rheumatoid arthritis patients than the healthy humans. In addition to reduction in pGSN, availability of actin and gelsolin-actin complexes in synovial fluids of the patients indicate depletion of gelsolin in clearing the actin complex from the affected joint [17, 18]. Gelsolin has also been identified as urinary peptide marker in early diagnosis of arthritis [19].

Table 1: Role of gelsolin in diseases.

S. No.	Disease	References
1.	Acute liver injury	[7]
2.	Acute liver injury, myocardial infarction, sepsis and myonecrosis	[8]
3.	Major trauma, Burn	[9], [10], [11], [12], [13], [31]
4.	Hemodialysis	[14]
5.	Inflammation induced lung injury	[15], [16]
6.	Rheumatoid arthritis	[17], [18], [19]
7.	Multiple sclerosis	[20], [21]
8.	Alzheimer's disease	[22], [23], [24]
9.	Tick-Borne Encephalitis and Lyme neuroborreliosis	[25]
10.	Malaria	[26], [27]
11.	Hyperoxia in mice	[28]
12.	Sepsis	[29], [30], [31]
13.	Diabetes	[32], [33], [34], [35]
14.	Stroke	[36], [38], [40]
15.	Traumatic Brain Injury	[39], [40]
16.	Physical exercise	[41]

7. Multiple sclerosis
Multiple sclerosis patients with idiopathic cephalgia, idiopathic facial nerve palsy and ischialgia due to discopathy showed notable fall in pGSN levels than the healthy controls. Outcome of the study propose that gelsolin is involved in chronic inflammatory lesions associated to neurodegeneration and also involved in diagnosis as well as treatment of this disease [20, 21].

8. Alzheimer's disease (AD)
Earlier studies have acknowledged the anti-amyloidogenic function of gelsolin in AD and this is one more pathological condition showing a decline in gelsolin levels in brain. Hirko *et al.*, 2007 [22] established that insignificant expression of plasma gelsolin is an appropriate gene-therapeutic shift in control of AD [22]. Gelsolin has also been proposed as therapy for Alzheimer disease as it can diminish amyloid load by inhibiting Abeta fibrillization, and acting as an antioxidant and anti-apoptotic protein [23]. Based on the results of some other studies where gelsolin levels were measured between slow cognitive declining AD patients, quick cognitive declining AD

patients (RCD) and non-demented subjects (NDS). Gelsolin values were considerably lower in AD patients in comparison to the NDC subjects. These outcomes suggested that gelsolin has some role in complex understanding of development of AD [24].

9. Tick-Borne Encephalitis and Lyme neuroborreliosis
In patients of tick-borne encephalitis and lyme neuroborreliosis, a decrease of pGSN levels was observed as compared to non- infected control as has also been reported previously, implicating gelsolin in the pathophysiology of an inflammatory response. Based on these studies it is proposed that gelsolin can be used in diagnosis as well as therapeutic purposes for TBE / LNB [25].

10. Malaria
Malaria is one of the very important infectious diseases caused by Plasmodium falciparum and is responsible for one million deaths per year. pGSN levels were measured in patients with malaria and was observed that mean pGSN levels were less than 50% of healthy control subjects. Since, there is

destruction of RBCs in malaria due to hemolysis, therefore, it might be the reason for the decline in pGSN levels in malaria. Further, when patients were treated with anti-malarial drugs, it was found that pGSN levels also return to normal levels [26]. Huang *et al.*, 1997 [27] also observed that pGSN levels were lower in case of malaria patients as compared to normal individuals, thereby proposing that gelsolin values can be used as early prognostic marker in malaria [11].

During comparison of serum protein profile of malaria patients and healthy individuals, many proteins like apolipoprotein, serum amyloid A, gelsolin, complement factor H and fibrinogen were found to differ. These proteins can be used as inflammation related biomarkers during malaria infection [27].

11. Hyperoxia in mice
Role of gelsolin as a therapeutic agent was investigated by Christofidu-Solomidou *et al.*, in 2002 [28] by inducing acute respiratory distress syndrome in mice by exposing mice to 95% O_2 for a total of 72 hours. Results showed a significant decrease in pGSN levels in hyperoxic mice. Further, exogenous administration gelsolin was able to negate consequential exudative reaction [28].

12. Sepsis
In a study of cecal ligation and double puncture model of sepsis in rats, decline in pGSN levels was observed. However, restoration of gelsolin levels by administration of human pGSN exogenously could bring the pGSN levels to the normal levels as well as reducing the morbidity in rats. Over all these facts further prove that gelsolin therapy can be effective in treatment of sepsis [29].

Role of gelsolin as a therapeutic agent was further investigated by Lee and co-workers in lipopolysaccharide (LPS, endotoxin) challenge or cecal ligation and puncture in mice. There was a decline of pGSN by 25-50% of normal in septic mice within 6 hrs of the inducing sepsis. Septic mice treated with exogenous administration of gelsolin showed 88% and 30% survivability in LPS treated mice and CLP challenged mice respectively. These results substantiate the protective role of gelsolin in sepsis in mice as gelsolin effectively was able to remove actin filaments from the circulation following septic challenge [30].

In yet another study of sepsis induced in C57BL/6 mice, a decrease in pGSN values was observed during sepsis [31]. Therapeutic efficacy of gelsolin has been checked in animal models of sepsis and burn in earlier studies. However, large amounts (~8 mg per rat/mouse) of exogenous gelsolin were used for treatment. Since, only N terminus portion of gelsolin has actin severing property, Peddada and co-workers made several truncated versions of plasma gelsolin, with more and faster capability of depolymerization of F-actin. Further, with use of smaller truncated versions of gelsolin, they were able to rescue septic mice with much lower dose (2 mg/ mouse) than the previously used dose (8 mg per mouse) [32].

13. Diabetes
Diabetes mellitus is a metabolic disease that occurs either defective production of insulin by the pancreas or due to resistance in proper utilization of insulin by the body. Review of literature suggested a role of gelsolin in insulin regulation via different pathways. Nelson *et al.*, in 1985 reported presence of gelsolin in insulin secreting cell lines of hamster [32]. A report in 2006 by Tomas *et al.*, suggested that F-actin restructuring preceding insulin discharge requires gelsolin and which is responsible for glucose-dependent MAPK signal

transduction with the intention of regulating beta-cell insulin secretion [33]. Over expression of PIP2 affects the F-actin remodeling and since PIP2 is also involved in regulation of functions of gelsolin, therefore, due to PIP2 mediated inactivation of Ca^{2+}-dependant gelsolin, responsible for increased vulnerability of β-cells to apoptosis [34]. In 2012, gelsolin has been shown to have a direct association with the N-terminal half of Syntaxin 4 (Syn4) and regulates insulin granule secretion via exocytosis [35]. Kalwat and co-workers showed a biphasic model of insulin secretion so as to inactive gelsolin clamps Syn4 from functioning, and Ca^{2+} activation of gelsolin leads to their dissociation in turn enabling Syn4 to facilitate insulin exocytosis [35].

14. Stroke
Infarct size increases in gelsolin–null mice than the control mice following reversible middle cerebral artery occlusion. Therefore, proposing a neuro-protective effect of gelsolin in stroke [36].

Protective role of gelsolin in ischemic brain injury was studied in wild type and gelsolin knockout mice treated with trichostatin A (TSA). Levels of filamentous actin were largely decreased by TSA pre-treatment in brain of wildtype but not gelsolin-deficient mice. Further, the mice were exposed to middle cerebral artery occlusion for 1 hour and subsequent reperfusion. The results showed that TSA pre-treated wild type mice showed significantly smaller brain lesions than the gelsolin deficient mice, thereby indicating that gelsolin is important in TSA treatment of cerebral ischemia in mice [37].

In 2011, Guo and co-workers studied alterations in pGSN levels and correlated prognosis of ischemic stroke in patients. The results showed significantly lowered pGSN values in stroke patients than normal controls. These workers further described pGSN an important complementary mean of predicting deaths due to stroke [38].

In traumatic brain injury (TBI), change in plasma gelsolin level was studied on admission and up to 7 days for understanding its correlation with the prognosis of the disease. Within 6 hour of brain injury, plasma gelsolin level declined rapidly and the levels were lowest at 24 hours in patients, the levels improved steadily subsequently, however, were considerably worse in comparison to healthy controls throughout the observation period, The study further concluded that these poor values of pGSN serves as prognostic indicator of death and restoration of normal level of gelsolin would be effective therapy for TBI [39, 40].

15. Physical exercise
Recently in a study Yu and co-workers proposed that that body's hormonal and metabolic adaptations to physical exercise are correlated to changes in the pGSN values. After a period of 30 min of exercise, pGSN levels of untrained healthy males showed a decline whereas levels were increased in endurance trained persons. However, even though this increase was not significant but endurance training because of the adaptation to exercise was able to enhance the expression of gelsolin [41].

16. Conclusion
This review has brought forward the significance of pGSN levels in several diseases of human as well as animal models of diseases. This further opens up the opportunities for use of gelsolin as a prognostic biomarker of health and as a potential therapeutic agent.

17. References

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