Review Article

Nicotinamide Riboside and its Potential Role in Curbing Cytokine Storm in COVID-19

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ABSTRACT

Whole world is reeling due to SARS-CoV-2 pandemic. Global cases of covid 19 are increasing day by day. Cytokine storm is the main culprit resulting in case fatality. Measures to prevent cytokine storm is the most prudent approach in treatment of COVID-19. PARP-1 in response to tissue damage, results in release of pro-inflammatory cytokines / chemokines. PARP-1 inhibitors have been tried in lung injuries. We present you a treatment perspective, nicotinamide as PARP-1 inhibitor, in the treatment of COVID-19. .

Key-words : COVID-19, SARS-CoV-2, Cytokine storm, PARP-1 inhibitor, Nicotinamide.

Introduction :

Nictotinamide riboside also known as niacinamide or Vitamin B3 is a Poly ADP ribose polymerase (PARP) inhibitor.[1,2] This inhibitory effect of nictoinamide on PARP -1, mitigates endotoxin , or oxidative stress related lung injury.[2] COVID-19 which is currently grappling the world is one form of acute lung injury due to cytokine storm, in its severe most form. Although majority of the cases are mild or moderate. Severe cases have ill effects of cytokine storm.

PARP inhibitors have showed beneficial effects in animal models of acute respiratory distress syndrome (ARDS), asthma and ventilator-induced lung injury. PARP inhibition may potentiate the effectiveness of Tocilizumab, therapy. PARP inhibitors therapy would benefit COVID-19 patients and trials on use of such drugs be started as soon as possible.[3]

Lung biopsy of deceased human victim of COVID-19 suggested induction of high level of expression of PARP and that boosting NAD+, which is depressed due to PARP-10 over expression, may restore antiviral PARP functions, through the nicotinamide and nicotinamide riboside kinase pathways to support innate immunity to SARS-CoV-2.[4] The pattern of PARP up regulation seen in SARS-CoV-2 infected tissue culture, infected ferrets and lung biopsy of human victim resembled closely.[4]

This again consolidates a new perspective in the treatment schema of SARS-CoV-2. It also gives clues for innate immunity against SARS-CoV-2. Out of several PARP, PARP-14 is required for the innate immunity against coronavirus in general and SARS-CoV-2 in particular.[5]

PARP : Role in lung injury

Protein ADP-ribosylation (PARP) is a reversible post-translational modification, which alters protein activity leading to alteration of cell signaling.[6] PARP-1 promotes inflammatory responses by positively regulating the pro-inflammatory NF- B transcription factors.[7]

Figure-1 explains the role of PARP as central stage in the release of pro-inflammatory cytokines, chemokines, growth factors.

PARP-1 is ubiquitously expressed and plays a central role in inflammation. By activating NF- B through several mechanisms (and also NFAT and AP1), PARP-1 induces the production of inflammatory (TNF , IL1 and others) and effector T cell cytokines (IL4, IL5). Inflammatory mediators activated by PARP-1 include metalloproteinases (MMP9), inducible nitric-oxide synthase (iNOS), several chemokines, prostaglandins (PGE2) and alarmins (HMGB1).[7]

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It also favours cell recruitment through upregulation of adhesion molecules, including selectins and cell adhesion molecules (ICAM, Intercellular Cell Adhesion Molecule; VCAM, Vascular Cell Adhesion Molecule). When over-activated, PARP-1 also induces cell death and tissue damage, further fueling the inflammatory process. On the other side, PARP-1 inhibits the expression of Foxp3, a transcription factor required for regulatory T cell differentiation and function, and of IL10, an inhibitory cytokine.[7]

Interestingly, PARP knockout mice did not show any up-regulation of all these pro-inflammatory cytokines, chemokines.

NFkB : Natural factor kappa B, NFAT : Nuclear factor of activated T-cells, AP-1 : Activator protein 1, TNF : Tumour necrosis factor , IL : Interleukins, IFN : Interferon , MMP-9 : Matrix metalloprotein-9, COX-2 : Cyclo-oxygenase-2, iNOS - Inducible nitric oxide synthetase, PGE-2 : Prostaglandin E-2, HMGB-1 : High Mobility Group Box 1, ICAM : Intercellular Cell Adhesion Molecule, VCAM : Vascular Cell Adhesion Molecule, FOXp3 : forkhead box P3.

PARP : Role in viral pneumonia

We know the fact that NK cells play pivotal role in the control of viral infections. PARP-1 is the important. PARP plays important role in development of inflammation. This is in response to any insult, done on lung parenchyma. Treatment

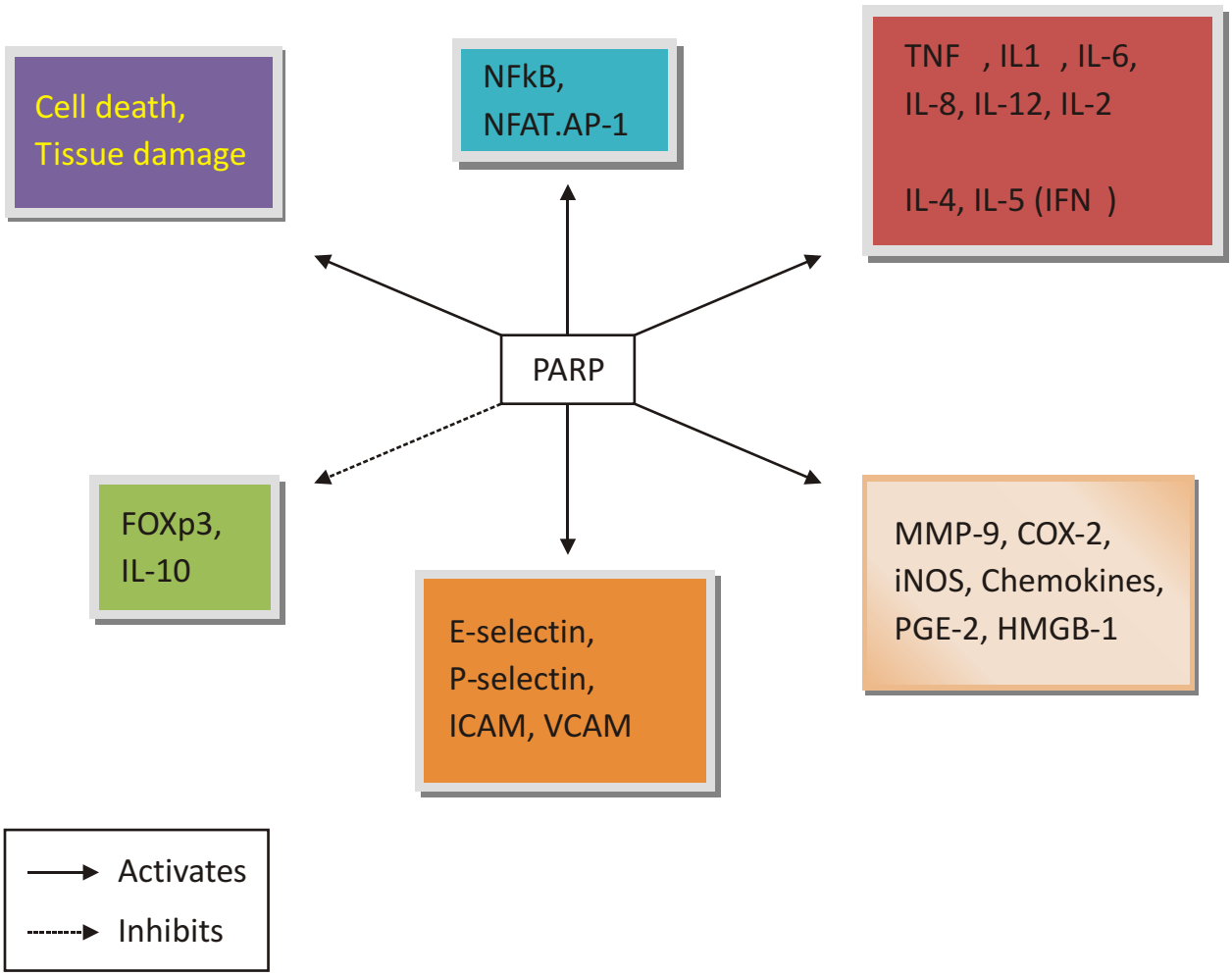

Figure 1 : **Showing role of PARP as inducer of pro-inflammatory**

with 10 mg/kg PARP-1 inhibitor in VV-infected mice led to a significant ($P < 0.01$) reduction in the total peritoneal NK cell numbers without obvious toxicity.[8]

PARP in SARS-CoV-2

PARP plays dominant role in the immune response of lung. PARP is known to have pathogenesis in mechanical Ventilator induced lung injury. (VILI).[9] PARP-1 inhibitor decreased the levels of IL-6 and active plasminogen activator inhibitor 1 in the lungs, attenuated leukocyte lung transmigration, and reduced pulmonary edema and apoptosis.[10]

Nicotinamide : a potential treatment perspective in COVID-19

In a study done on mice, vitamin B3, also known as nicotinamide, enhanced the killing of Staphylococcus aureus through a myeloid-specific transcription factor and vitamin B3 was efficacious in both prophylactic and therapeutic settings.[11] Nicotinamide has a potent immunomodulatory effect in vitro, and may have great potential for treatment of human inflammatory disease. Nicotinamide in vitro studies and models to represent endotoxaemia reveals that nicotinamide decreases cytokines such as IL-6, in a dose dependent manner.[12]

As shown in ***Table 1,*** nicotinamide exerts its anti-inflammatory role in a dose dependent manner and although most of the studies were done on invitro models or are pre-clinical, they undoubtedly prove the anti-inflammatory role of nicotinamide.

In vivo studies on nicotinamide suggested that higher dose of nicotinamide is required to possibly inhibit PARP-1 in the whole organism. Nicotinamide as a precursor of NAD+, ATP, and as an endogenous inhibitor of PARP-1 therefore plays significant roles in cellular protection and in determining cellular fate in response to genotoxic DNA damage.[17]

Table 1 : **Shows anti-inflammatory properties of nicotinamide - a amide derivative of vitamin B3[12]**

1	**Inhibition of inducible NO synthase (iNOS)[13]**
2	Free radical scavenging[14]
3	Suppression of MHC class II expression[15]
4	Intracellular adhesion molecule ICAM-1 expression on endothelial cells[16]
5	Inhibit poly (ADP ribose) polymerase (PARP)[17]

High dose Nicotinamide : dose, safety, drug interaction, pharamcokinetics, pharmacodynamics

The recommended daily intake of nicotinamide is 20 mg a day for an adult . Whereas the dose used to treat a diabetic and pre-diabetic patients has ranged from 25- 50 mg/kg /day . (1.75-3.5 g/day) . such high dose require toxicological scrutiny. High-dose nicotinamide should still, however, be considered as a drug with toxic potential at adult doses in excess of 3 gm/day and unsupervised use should be discouraged.[17]

Table 2 : **Side effects[18]**

1	**Hepatotoxcity - reversible**
2	Minor degree of insulin resistance
3	Islet tumour formation - seen in rats / not reported in humans

Table 3 : **Pharmacokinetics of nicotinamide[18]**

Absorption	**Readily absorbed parenterally and all parts of GI tract.**
Peak plasma concentrations	1 hour of oral ingestion
Distribution	Distributed in all tissues
Clearance	High hepatic extraction ratio and plasma clearance
Metabolism	At high doses methylated to n methyl nicotinamide - which is oxidised in liver to n-methyl 2 pyridone - 5 carboxilic acid amide (2 pyr) Even oxidation to nicotinamide n-oxide

Table 4 : **Toxicity**[18]

Toxicity	Human data
Liver toxicity	Jaundice with a frequency of 1: 2000
Teratogenicity	No evidence
Oncogencity	No evidence
Growth retardation	No growth retardation
Insulin response	25 mg/kg (1.2 g/m2) - no effect in normal subject. 25mg/kg : 1 gm/day improved stimulated C peptide secretion in newly diagnosed type-1 diabetic patients. 1.2 gm/m2 dose decreased first phase insuln response in pre-diabetic subjects.

Table 5 : **Side effects of high dose nicotinamide** [18]

Side effects	Frequency
Flushing	**≤1.5%**
Facial erythema	**≤0.5%**
Hives	**≤0.4%**
Sore mouth	**≤0.4%**
Dull headache	**≤0.5%**
Heartburn	**≤1.6%**
Nausea (with radiotherapy)	**17-65%**
Nausea (without radiotherapy)	**≤1.5%**
Other gastrointestinal symptoms	**≤0.8%**
Inability to focus the eyes	**≤0.4%**
Dry hair	**≤0.4%**
Fatigue	**≤0.4%**

ENDIT : European Nicotinamide Diabetes Intervention Trial[19]

ENDIT although didn't show any benefit in prevention of type 1 diabetes in individuals at a dose of 1.2 g/m2. But at that high dose of nicotinamide, there were no much serious side effects, thus high dose of nicotinamide although a bit toxic, should be taken under supervision.

Drug interaction

Nicotinamide inhibit CYP2D6, CYP3A4 and CYP2E1[20]. So caution must be exercised while using drugs acting on these cytochrome pathway.

Trials on nicotinamide for COVID-19

University of Copenhagen has sponsored a randomised double blind, case control, phase 2 trial on nicotinamide in elderly Covid-19 patients (> 70 yr) This, randomized double blinded case-control trial, the investigators will treat elderly (> 70 year old) Covid-19 patients with 1 g of nicotinamide riboside or placebo for 2 weeks and investigate if this affects the clinical course of the disease.

Conclusion :

We need a large scale trial to contain cytokine storm in elderly population. Elderly as we know have slow metabolism due to aging and this leads to nicotinamide deficiency - putting them at risk of severe Covid-19 infection. Adding to their woes is the presence of co-morbidity like diabetes, hypertension, etc which slows down the metabolism further. So nicotinamide supplementation albeit at high dose in elderly patients be studied at large scale. Such trial will give us an insight on wide spread subclinical nicotinamide deficiency in the susceptible population. At present nicotinmaide supplementation and its role in Covid-19 is a perspective, but if studied it can become a panacea for COVID-19!.

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