Inducible Nitric Oxide Synthase (iNOS) and Kidney Research Literatures

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Abstract: Nitric oxide synthases (NOSs, EC 1.14.13.39) are a family of enzymes catalyzing the production of nitric oxide (NO) from L-arginine. NO is an important cellular signaling molecule that helps to modulate the vascular tone, insulin secretion, airway tone and peristalsis, etc, and NO is involved in angiogenesis and neural development. It may function as a retrograde neurotransmitter. NO is mediated in mammals by the calcium-calmodulin controlled isoenzymes eNOS (endothelial NOS) and nNOS (neuronal NOS). The inducible isoform, iNOS, is involved in immune response, binds calmodulin at physiologically relevant concentrations, and produces NO as an immune defense mechanism, as NO is a free radical with an unpaired electron. It is the proximate cause of septic shock and may function in autoimmune disease. NOS isoforms catalyze other leak and side reactions, such as superoxide production at the expense of NADPH. As such, this stoichiometry is not generally observed, and reflects the three electrons supplied per NO by NADPH.
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1. Introduction

Nitric oxide synthases (NOSs, EC 1.14.13.39) are a family of enzymes catalyzing the production of nitric oxide (NO) from L-arginine. NO is an important cellular signaling molecule that helps to modulate the vascular tone, insulin secretion, airway tone and peristalsis, etc, and NO is involved in angiogenesis and neural development. It may function as a retrograde neurotransmitter. NO is mediated in mammals by the calcium-calmodulin controlled isoenzymes eNOS (endothelial NOS) and nNOS (neuronal NOS). The inducible isoform, iNOS, is involved in immune response, binds calmodulin at physiologically relevant concentrations, and produces NO as an immune defense mechanism, as NO is a free radical with an unpaired electron. It is the proximate cause of septic shock and may function in autoimmune disease. NOS isoforms catalyze other leak and side reactions, such as superoxide production at the expense of NADPH. As such, this stoichiometry is not generally observed, and reflects the three electrons supplied per NO by NADPH.

The following introduces recent reports as references in the related studies.

Anuar, F., M. Whiteman, et al. "Nitric oxide-releasing flurbiprofen reduces formation of proinflammatory hydrogen sulfide in lipopolysaccharide-treated rat." Br J Pharmacol. 2006 Apr;147(8):966-74.

The biosynthesis of both nitric oxide (NO) and hydrogen sulfide (H2S) is increased in lipopolysaccharide (LPS)-injected mice and rats but their interaction in these models is not known. In this study we examined the effect of the NO donor, nitroflurbiprofen (and the parent molecule flurbiprofen) on NO and H2S metabolism in tissues from LPS-pretreated rats. Administration of LPS (10 mg kg(-1), i.p.; 6 h) resulted in an increase (P<0.05) in plasma TNF-alpha, IL-1beta and nitrate/nitrite (NO(x)) concentrations, liver H2S synthesis (from added cysteine), CSE mRNA, inducible nitric oxide synthase (iNOS), myeloperoxidase (MPO) activity (marker for neutrophil infiltration) and nuclear factor-kappa B (NF-kappaB) activation. Nitroflurbiprofen (3-30 mg kg(-1), i.p.) administration resulted in a dose-dependent inhibition of the LPS-mediated increase in plasma TNF-alpha, IL-1beta and NO(x) concentration, liver H2S synthesis (55.00+/-0.95 nmole mg protein(-1), c.f. 62.38+/-0.47 nmole mg protein(-1), n = 5, P<0.05), CSE mRNA, iNOS, MPO activity and NF-kappaB activation. Flurbiprofen (21 mg kg(-1), i.p.) was without effect. These results show for the first time that nitroflurbiprofen downregulates the biosynthesis of proinflammatory H2S and suggest that such an effect may contribute to the augmented anti-inflammatory activity of this compound. These data also highlight the existence of 'crosstalk' between NO and H2S in this model of endotoxic shock.

Aroor, A. R., S. McKarns, et al. "Maladaptive immune and inflammatory pathways lead to cardiovascular insulin resistance." Metabolism. 2013 Nov;62(11):1543-52. doi: 10.1016/j.metabol.2013.07.001. Epub 2013 Aug 8.

Insulin resistance is a hallmark of obesity, the cardiorenal metabolic syndrome and type 2 diabetes mellitus (T2DM). The progression of insulin resistance increases the risk for cardiovascular disease

(CVD). The significance of insulin resistance is underscored by the alarming rise in the prevalence of obesity and its associated comorbidities in the Unites States and worldwide over the last 40-50 years. The incidence of obesity is also on the rise in adolescents. Furthermore, premenopausal women have lower CVD risk compared to men, but this protection is lost in the setting of obesity and insulin resistance. Although systemic and cardiovascular insulin resistance is associated with impaired insulin metabolic signaling and cardiovascular dysfunction, the mechanisms underlying insulin resistance and cardiovascular dysfunction remain poorly understood. Recent studies show that insulin resistance in obesity and diabetes is linked to a metabolic inflammatory response, a state of systemic and tissue specific chronic low grade inflammation. Evidence is also emerging that there is polarization of macrophages and lymphocytes towards a pro-inflammatory phenotype that contributes to progression of insulin resistance in obesity, cardiorenal metabolic syndrome and diabetes. In this review, we provide new insights into factors, such as, the renin-angiotensin-aldosterone system, sympathetic activation and incretin modulators (e.g., DPP-4) and immune responses that mediate this inflammatory state in obesity and other conditions characterized by insulin resistance.

Asakura, H., R. Asamura, et al. "Selective inducible nitric oxide synthase inhibition attenuates organ dysfunction and elevated endothelin levels in LPS-induced DIC model rats." J Thromb Haemost. 2005 May;3(5):1050-5.

We examined the role of nitric oxide (NO) produced by an inducible isoform of NO synthase (iNOS) using N[6]-(iminoethyl)-lysine (L-NIL), a selective iNOS inhibitor, in the rat model of lipopolysaccharide (LPS)-induced disseminated intravascular coagulation (DIC) and investigated changes in organ function, plasma levels of NOX (metabolites of NO) and endothelin. We induced experimental DIC by the sustained infusion of 30 mg kg(-1) LPS for 4 h via the tail vein. We then investigated the effect of L-NIL (6 mg kg(-1), from -0.5 to 4 h) on LPS-induced DIC. Blood was withdrawn at 4 and 8 h, and all four groups (LPS with or without L-NIL at 4 and 8 h) consisted of eight rats. Three of the animals in the 8-h LPS group died, and we examined blood samples from five rats in this group. None of the other rats died. The LPS-induced elevation of creatinine, alanine aminotransferase, glomerular fibrin deposition and plasminogen activator inhibitor was significantly suppressed by L-NIL coadministration, although L-NIL did not affect the platelet count, fibrinogen concentration or the level of thrombin-antithrombin complex. Moreover, plasma levels of the D-dimer that reflect the lysis of cross-linked fibrin were significantly increased by L-NIL coadministration in the LPS-induced DIC model. Plasma levels of NOX and endothelin were obviously increased by LPS infusion. However, both levels were significantly suppressed in the LPS + L-NIL group, when compared with the LPS group. Although mean arterial pressure (MAP) was significantly decreased between 2 and 8 h compared with the control in the LPS group, this depression was significantly attenuated in the LPS + L-NIL group. Our results suggest that NO induced by iNOS contributes to hypotension (depressed MAP), the progression of hepatic and renal dysfunction, microthrombus deposition and elevated endothelin levels in the rat model of LPS-induced DIC.

Bultinck, J., P. Sips, et al. "Systemic NO production during (septic) shock depends on parenchymal and not on hematopoietic cells: in vivo iNOS expression pattern in (septic) shock." FASEB J. 2006 Nov;20(13):2363-5. Epub 2006 Oct 4.

Septic shock is the leading cause of death in noncoronary intensive care units and the 10th leading cause of death overall. Several lines of evidence support an important role for the vasodilator NO in hypotension, a hallmark of septic shock. However, NO may also positively or negatively regulate inflammation, apoptosis, and oxidative stress. These dual effects of NO may relate to its isoform specific production but also to differences in cellular and/or temporal expression. Via bone marrow transplantations, we examined the contribution of hematopoietic cells to the dramatically elevated NO levels seen in (septic) shock. Surprisingly, hematopoietic cells are not responsible at all for the production of circulating NO after systemic tumor necrosis factor or lipopolysaccharide challenge and contribute only marginally in a bacteremic (Salmonella) model of septic shock. Immunohistochemistry identified the nonhematopoietic sources of NO as hepatocytes, paneth cells, and intestinal and renal epithelial cells. In contrast, during granulomatous Bacillus Calmette-Guerin inflammation, the hematopoietic cell population represents the sole source of systemic NO. These mouse data demonstrate that, in contrast to the general conjecture, the dramatically elevated levels of NO during (septic) shock are not produced by hematopoietic cells such as monocytes/macrophages but rather by parenchymal cells in liver, kidney and gut.

Cartwright, N., O. Murch, et al. "Selective NOD1 agonists cause shock and organ injury/dysfunction in

vivo." Am J Respir Crit Care Med. 2007 Mar 15;175(6):595-603. Epub 2007 Jan 18.

RATIONALE: NLRs (nucleotide oligomerisation domain [NOD] proteins containing a leucine-rich repeat) are cytosolic pattern recognition receptors. NOD1 senses diaminopimelic acid-containing peptidoglycan present in gram-negative bacteria, whereas NOD2 senses the muramyl dipeptide (MDP) present in most organisms. Bacteria are the most common cause of septic shock, which is characterized clinically by hypotension resistant to vasopressor agents. In animal models, gram-negative septic shock is mimicked by lipopolysaccharide (LPS), which signals through Toll-like receptor 4 (TLR4) and its adaptor MyD88. The role of NLRs in the pathophysiology of septic shock is not known. OBJECTIVES: To compare the effects of selective NOD1 agonists with LPS in vivo. METHODS: Vascular smooth muscle cells or whole aortas from wild-type or genetically modified mice were stimulated in vitro with agonists of NOD1 (FK565) or NOD2 (MDP). Vasoconstriction was measured using wire myography. Nitric oxide (NO) formation was measured using Griess reaction and NO synthase-II protein by Western blotting. In vivo, blood pressure, heart rate, and urine output were measured in sham-, LPS-, or FK565-treated animals. Biomarkers of end-organ injury, coagulation activation, NO, and cytokines were measured in plasma. MAIN RESULTS: FK565, but not MDP, induced NO synthase-II protein/activity in vascular smooth muscle and vascular hyporeactivity to pressor agents. FK565 had no effect on vessels from NOD1(-/-) mice, but was active in vessels from TLR4(-/-), TLR2(-/-), or MyD88(-/-) mice. FK565 induced hypotension, increased heart rate, and caused multiple (renal, liver) injury and dysfunction in vivo. CONCLUSIONS: Activation of NOD1 induces shock and multiple organ injury/dysfunction.

Cauwels, A., J. Bultinck, et al. "Dual role of endogenous nitric oxide in tumor necrosis factor shock: induced NO tempers oxidative stress." Cell Mol Life Sci. 2005 Jul;62(14):1632-40.

Tumor necrosis factor (TNF) is involved in pathologies like septic shock, inflammatory bowel disease and rheumatoid arthritis. TNF and lipopolysaccharide can incite lethal shock, in which cardiovascular collapse is centrally orchestrated by the vasodilating free radical nitric oxide (NO). However, NO synthase (NOS) inhibition causes increased morbidity and/or mortality, suggesting a dual role for NO. To investigate the potential protective role of NO during TNF shock, we treated mice with TNF with or without NOS inhibition. Experiments in endothelial-NOS- and inducible NOS-deficient mice identified inducible NOS as the source of protective NO. Distinctive TNF-induced lipid peroxidation, especially in liver and kidney, was aggravated by NOS inhibition. In addition, various antioxidant treatments and a phospholipase A2 (PLA2) inhibitor prevented sensitization by NOS inhibition. Together, these in vivo results indicate that induced NO not only causes hemodynamic collapse, but is also essential for curbing TNF-induced oxidative stress, which appears to hinge on PLA2-dependent mechanisms.

Escames, G., L. C. Lopez, et al. "Age-dependent lipopolysaccharide-induced iNOS expression and multiorgan failure in rats: effects of melatonin treatment." Exp Gerontol. 2006 Nov;41(11):1165-73. Epub 2006 Oct 17.

Senescence amplifies the sensitivity to endotoxemia, which correlates with increased nitric oxide (NO) levels and mortality. Melatonin displays antioxidant and anti-inflammatory effects, but its levels decrease with age. Lipopolysaccharide (LPS) (10 mg/kg) was injected to 3- and 18-month-old rats 6 h before they were killed, and melatonin (60 mg/kg) was injected before and/or after LPS. Inducible nitric oxide synthase (iNOS) expression and activity, nitrite content, lipoperoxidation (LPO) levels, and serum markers of liver, renal, and metabolic dysfunction, were measured in liver and lung of these animals. An age-dependent increase in iNOS activity, NO content, and LPO levels was observed, and these changes were augmented further by LPS. Melatonin decreased the expression and activity of iNOS, reducing NO and LPO levels to basal values in both septic LPS-treated groups. Liver, kidney, and metabolic dysfunctions were also significantly higher in aged that in young rats and further increased by LPS. Melatonin treatment counteracted these alterations in young and aged septic rats. Melatonin reduced LPS-dependent iNOS expression and multiorgan failure in a similar extent in young and aged rats. Because aged rats showed higher organ and metabolic impairment than young animals in response to LPS, the results also suggest an increased efficacy of the anti-septic properties of melatonin in the aged animals.

Heemskerk, S., J. G. Peters, et al. "Regulation of P-glycoprotein in renal proximal tubule epithelial cells by LPS and TNF-alpha." J Biomed Biotechnol. 2010;2010:525180. doi: 10.1155/2010/525180. Epub 2010 Mar 9.

During endotoxemia, the ATP-dependent drug efflux pump P-glycoprotein (Abcb1/P-gp) is upregulated in kidney proximal tubule epithelial cells. The signaling pathway through which lipopolysaccharide (LPS) or tumor necrosis factor-alpha (TNF-alpha) regulates P-gp expression and

activity was investigated further in the present study. Exposure of rat kidney proximal tubule cells to TNF-alpha alone or TNF-alpha and LPS increased P-gp gene and protein expression levels and efflux activity, suggesting de novo P-gp synthesis. Upon exposure to TNF-alpha in combination with LPS, P-gp activity in renal proximal tubule cells is increased under influence of nitric oxide (NO) produced by inducible NO synthase. Upon exposure to TNF-alpha alone, P-gp upregulation seems to involve TLR4 activation and nuclear factor kappaB (NF-kappaB) translocation, a pathway that is likely independent of NO. These findings indicate that at least two pathways regulate P-gp expression in the kidney during endotoxemia.

Kagota, S., Y. Yamaguchi, et al. "Chronic nitric oxide exposure alters the balance between endothelium-derived relaxing factors released from rat renal arteries: prevention by treatment with NOX-100, a NO scavenger." Life Sci. 2004 Apr 16;74(22):2757-67.

We investigated whether nitric oxide (NO) exposure alters the balance between NO and endothelium-derived hyperpolarizing factor (EDHF) released from rat renal arteries. To produce states of acutely or chronically excessive NO, lipopolysaccharide (LPS) was administered intraperitoneally to rats in a single dose of 4 mg/kg (LPS-single group) or in stepwise doses of 0.5, 1.0 and 2.0 mg/kg every other day (LPS-repeated group). On the day after LPS treatment, the protein levels of inducible NO synthase (iNOS) and endothelial NOS (eNOS) were measured, and the relaxation responses were determined in the renal arteries. The protein levels of iNOS markedly increased in both LPS-treated groups, while those of eNOS significantly increased in the LPS-repeated group compared with those in the respective control groups. In both LPS-treated groups, the relaxations in response to acetylcholine (ACh) and sodium nitroprusside remained unchanged. The ACh-induced relaxations in the presence of N(G)-nitro-L-arginine methyl ester, a NOS inhibitor, or by 1H-[1, 2, 4-] oxadiazole [4, 3-a] quinoxalin-1-one, a soluble guanylyl cyclase inhibitor, i.e. EDHF-mediated relaxations were significantly impaired in the LPS-repeated group but not in the LPS-single group, indicating increase in NO-mediated relaxation in the LPS-repeated group. These changes in the protein levels and EDHF-mediated relaxations induced by ACh observed in the LPS-repeated group were restored by treatment with NOX-100, a NO scavenger. These results suggest that persistent but not acute excessive NO exposure in rats impairs EDHF-mediated relaxation in renal arteries, leading to a compensatory upregulation of the eNOS/NO pathway.

Martini, S., S. Kramer, et al. "S1P modulator FTY720 limits matrix expansion in acute anti-thy1 mesangioproliferative glomerulonephritis." Am J Physiol Renal Physiol. 2007 Jun;292(6):F1761-70. Epub 2007 Mar 13.

FTY720 is a novel immune modulator whose primary action is blood lymphocyte depletion through interaction with sphingosine-1-phosphate (S1P) receptors. The present study analyzes the effect of FTY720 on both the early mesangial cell injury and the subsequent matrix expansion phase of experimental mesangioproliferative glomerulonephritis. Disease was induced by injection of OX-7 anti-thy1 antibody into male Wistar rats. In both protocols, FTY720 administration (0.3 mg/kg body wt) resulted in a selective and very marked reduction in blood lymphocyte count. In the injury experiment, the S1P receptor modulator was given starting 5 days before and continued until 1 day after antibody injection. FTY720 did not significantly affect the degree of anti-thy1-induced mesangial cell lysis and glomerular-inducible nitric oxide production. In the matrix expansion experiment, FTY720 treatment was started 1 day after antibody injection and continued until day 7. In this protocol, the S1P modulator reduced proteinuria, histological matrix expansion, and glomerular protein expression of TGF-beta(1), fibronectin, and PAI-1. Glomerular collagen III staining intensity was decreased. FTY720 reduced markedly glomerular lymphocyte number per cross section and to a lesser degree macrophage infiltration. In conclusion, FTY720 significantly limits TGF-beta(1) overexpression and matrix protein expression following induction of acute anti-thy glomerulonephritis, involving reductions in blood and glomerular lymphocyte numbers. The results suggest that lymphocytes actively contribute to matrix expansion in experimental mesangioproliferative glomerulonephritis. Our study expands on findings on FTY720's beneficial effects on tubulointerstitial and functional disease progression previously reported in anti-thy1-induced chronic glomerulosclerosis.

Porst, M., A. Hartner, et al. "Inducible nitric oxide synthase and glomerular hemodynamics in rats with liver cirrhosis." Am J Physiol Renal Physiol. 2001 Aug;281(2):F293-9.

This study was designed to test the hypothesis that glomerular de novo expression of inducible nitric oxide synthase (iNOS) contributes to renal hemodynamic abnormalities in liver cirrhosis developed 3 wk after common bile duct ligature (CBDL). De novo expression of iNOS mRNA was detected by RT-PCR in RNA extracts from isolated CBDL rat glomeruli whereas no iNOS mRNA was found in control rat glomerular RNA.

Immunohistochemical staining for iNOS was negative in control animals whereas, in CBDL rats, positive iNOS staining was detected in an apparently mesangial pattern in all glomeruli. Western blots of protein extracts from isolated glomeruli of CBDL rats, but not control animals, showed a prominent iNOS band of 130 kDa. Mean arterial pressure (MAP), renal plasma flow (RPF; p-aminohippurate clearance), and glomerular filtration rate (GFR; inulin clearance) were unaltered in CBDL rats, but the application of 4 mg/kg L-N(6)-(1-iminoethyl)lysine, a specific inhibitor of iNOS, reduced GFR and RPF significantly in CBDL rats, whereas control animals were not affected. Similar results were obtained with lipopolysaccharide (LPS)-pretreated animals, which were studied as a positive control for iNOS expression and as a model for recent iNOS induction.

Strub, A., W. R. Ulrich, et al. "The novel imidazopyridine 2-[2-(4-methoxy-pyridin-2-yl)-ethyl]-3H-imidazo[4,5-b]pyridine (BYK191023) is a highly selective inhibitor of the inducible nitric-oxide synthase." Mol Pharmacol. 2006 Jan;69(1):328-37. Epub 2005 Oct 13.

We have identified imidazopyridine derivatives as a novel class of NO synthase inhibitors with high selectivity for the inducible isoform. 2-[2-(4-Methoxy-pyridin-2-yl)-ethyl]-3H-imidazo[4,5-b]pyridine (BYK191023) showed half-maximal inhibition of crudely purified human inducible (iNOS), neuronal (nNOS), and endothelial (eNOS) NO synthases at 86 nM, 17 microM, and 162 microM, respectively. Inhibition of inducible NO synthase was competitive with l-arginine, pointing to an interaction of BYK191023 with the catalytic center of the enzyme. In radioligand and surface plasmon resonance experiments, BYK191023 exhibited an affinity for iNOS, nNOS, and eNOS of 450 nM, 30 microM, and >500 microM, respectively. Inhibition of cellular nitrate/nitrite synthesis in RAW, rat mesangium, and human embryonic kidney 293 cells after iNOS induction showed 40- to 100-fold higher IC(50) values than at the isolated enzyme, in agreement with the much higher l-arginine concentrations in cell culture media and inside intact cells. BYK191023 did not show any toxicity in various rodent and human cell lines up to high micromolar concentrations. The inhibitory potency of BYK191023 was tested in isolated organ models of iNOS (lipopolysaccharide-treated and phenylephrine-precontracted rat aorta; IC(50) = 7 microM), eNOS (arecaidine propargyl ester-induced relaxation of phenylephrine-precontracted rat aorta; IC(50) > 100 microM), and nNOS (field-stimulated relaxation of phenylephrine-precontracted rabbit corpus cavernosum; IC(50) > 100 microM). These data confirm the high selectivity of BYK191023 for iNOS over eNOS and nNOS found at isolated enzymes.

Yamamoto, F., Y. Ohgari, et al. "The role of nitric oxide in delta-aminolevulinic acid (ALA)-induced photosensitivity of cancerous cells." Biochem Biophys Res Commun. 2007 Feb 16;353(3):541-6. Epub 2006 Dec 22.

Application of delta-aminolevulinic acid (ALA) results in the endogenous accumulation of protoporphyrin IX and is a useful approach in the photodynamic therapy (PDT) of cancers. To investigate the role of nitric oxide (NO) in the specific accumulation of protoporphyrin and ALA-induced PDT of cancerous cells, we transfected inducible-nitric oxide synthase (NOS2) cDNA into human embryonic kidney (HEK) 293T cells and examined the ALA-induced photo-damage as well as the accumulation of porphyrin in the cells. When the NOS2-expressing HEK293T cells were treated with ALA and then exposed to visible light, they became more sensitive to the light with accumulating porphyrins, as compared with the ALA-treated control cells. An increase in the generation of NO in transfected cells led to the accumulation of protoporphyrin with a concomitant decrease of ferrochelatase, the final step enzyme of heme biosynthesis. When mouse macrophage-like RAW264.7 cells were cultured with lipopolysaccharide and interferon-gamma, the expression of NOS2 was induced. The addition of ALA to these cells led to the accumulation of protoporphyrin and cell death upon exposure to light. The treatment of cells with an NOS inhibitor, NG-monomethyl-L-arginine acetate, resulted in the inhibition of protoporphyrin accumulation and cell death.

Zager, R. A., A. C. Johnson, et al. "'Endotoxin tolerance': TNF-alpha hyper-reactivity and tubular cytoresistance in a renal cholesterol loading state." Kidney Int. 2007 Mar;71(6):496-503. Epub 2007 Jan 17.

The term 'endotoxin tolerance' defines a state in which prior endotoxin (lipopolysaccharide (LPS)) exposure induces resistance to subsequent LPS attack. However, its characteristics within kidney have not been well defined. Hence, this study tested the impact of LPS 'preconditioning' (LPS-PC; 18 or 72 h earlier) on: (i) selected renal inflammatory mediators (tumor necrosis factor (TNF)-alpha, interleukin-10 (IL-10), monocyte chemotactic protein-1 (MCP-1), inducible nitric oxide synthase (iNOS), Toll-like receptor 4 (TLR4); protein or mRNA); (ii) cholesterol homeostasis (a stress reactant); and (iii) isolated proximal tubule (PT) vulnerability to hypoxia or

membrane cholesterol (cholesterol oxidase/esterase) attack. Two hours post LPS injection, LPS-PC mice manifested reduced plasma TNF-alpha levels, consistent with systemic LPS tolerance. However, in kidney, paradoxical TNF-alpha hyper-reactivity (protein/mRNA) to LPS existed, despite normal TLR4 protein levels.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

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