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MOLECULAR MECHANISMS REGULATING iNOS EXPRESSION IN VARIOUS CELL TYPES

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Inducible nitric oxide synthase (iNOS) has been shown to be present in a variety of cell types, and nitric oxide (NO) has been implicated in a multitude of biological functions. The purpose of this review is twofold: (1) to provide a comprehensive table of cell types that produce NO together with the effects of agents used to study iNOS regulation, as a ready reference for the investigators in the field; and (2) to summarize recent observations dealing with iNOS signal transduction mechanisms. Initially, the major regulation of NO production was believed to occur at the transcription step, but now it is recognized that NO regulation can occur at the transcriptional, posttranscriptional, translational, and posttranslational level. There have been a number of studies of the regulation of iNOS in various cell types, often yielding conflicting results. The major emphasis of this review is on iNOS signal transduction mechanisms. For example, the role of JAK kinases and mitogen-activated protein (MAP) kinases in iNOS regulation is elaborated. In addition, species differences in the iNOS promoter region and the role of RNA structure in iNOS expression is discussed. The role MAP kinases play in translational regulation in addition to transcriptional regulation is emphasized. An analysis of the current data and suggestions for future studies are also presented.

Stuehr and Marletta (1985) demonstrated that nitrite and nitrate are produced in murine macrophages. These compounds have been shown to be the end products of nitric oxide synthesis in cells. Nitric oxide (NO) is synthesized by a family of three NO synthases (NOS). The three isoforms of this enzyme, neuronal (nNOS), inducible (iNOS), and endothelial (eNOS), are products of three genes named *NOS1, NOS2,* and *NOS3,* respectively (Moncada et al., 1997). Although nNOS and eNOS do exhibit a modest degree of regulation at the expression level, iNOS is the major isoform and is expressed in most cells only after induction by immunologic or inflammatory stimuli. In view of the profound effects attributed to NO in various pathological and physiological conditions, an understanding of the regulation of NO production in tissues has become an important research area. Within the last few years, various laboratories have focused extensively on the various signal transduction mechanisms involved in regulating iNOS expression. iNOS, originally purified and cloned from an immunoactivated macrophage cell line, has now been identified in numerous other cell types. The diversity of cell types that are capable of producing iNOS appears to have introduced

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additional complexity in the elucidation of signal transduction mechanisms involved in regulating iNOS expression. Seemingly contradictory results are being reported from various laboratories with respect to various second messengers involved in the regulation of iNOS expression. However, these diverse findings suggest that iNOS may be regulated differently in different cell types (Table 1). In addition, the effects of agents used to modify NO formation may depend largely upon the nature of the stimuli that are being used to activate the particular cell type. Thus, the apparent contradictions may actually be revealing the diverse ways by which iNOS expression are regulated in various cell types. The existing data on the molecular mechanisms involved in the regulation of iNOS expression are summarized in this review. This will hopefully serve to introduce a semblance of order into a chaotic state of knowledge in this important area of investigation.

In Table 1 a list of cell types, the species from which the cells were obtained, the stimuli used to induce iNOS, and the agents used to modify the iNOS induction are listed. The intracellular signal molecules implicated in the modulation of iNOS are also listed where applicable. Thus, this table provides a quick reference to various cell types used and how the same agent may produce a different effect depending upon the cell type and the stimulus used.

Regulation of iNOS differs with strain (Hussain & Qureshi, 1998) and species (Adler et al., 1995; Jungi et al., 1996; Jesch et al., 1997). The expression of iNOS in bovine, goat, hamster, human, monkey, murine, pig, and rabbit macrophages has been reported. The macrophage response to various cytokines and the extent of the response differs considerably according to the species. Goat, hamster, monkey, human, and pig macrophages are relatively resistant to iNOS production in response to cytokine stimulation, whereas bovine and murine macrophages generate considerable amounts of iNOS under similar conditions (Jungi et al., 1996). Therefore it is important to note which strain and species are being used in any particular study. The same agent may have different effects, depending on the cell type and the species being studied. This has been well documented with regard to regulation of NO production by transforming growth factor-β1 (TGF-β1), as reviewed by Vodovotz (1997). TGF-β suppresses iNOS expression by three distinct mechanisms: decreased stability and translation of iNOS mRNA, and increased degradation of iNOS protein. This was the first evidence that iNOS was subject to other than transcriptional regulation (Vodovotz et al., 1993). Subsequent studies have shown that iNOS is regulated at transcriptional, posttranscriptional, translational, and posttranslational levels. Recent developments in these areas are reviewed with emphasis on signal transduction mechanisms that have been proposed in various cell types.

iNOS GENE PROMOTER

The molecular mechanisms for the transcriptional regulation of the iNOS gene have been studied by cloning mouse (Lowenstein et al., 1993;

TABLE 1. NO Production in Different Cell Types from Different Species and Agents Used for Studying Regulation

Cell type	Species	Stimulus	Agent	Effect on NO	Intracellular mechanism	Reference
Connective tissue						
Fibroblasts (L929)	Mouse	IFN-γ	Pentoxifylline	↑	Phosphodiesterases	Stosic-Grujicic et al. (1998)
Fibroblasts (lung)	Rat	IL-1β/IFN-γ	Dexamethasone	↓		Jorens et al. (1992)
Fibroblasts (embryonic and lung)	Rat and mouse	IL-1β/TNF				Lavnikova and Laskin (1995)
Fibroblasts (Swiss 3T3)	Mouse	1. LPS 2. PMA	1. TGF-β 2. TGF-β	↑ ↑		Gilbert and Herschman (1993)
Dermal						
Keratinocyte	Human	TNF/IL-1β				Sirsjo et al. (1996)
Keratinocyte (HaCat cell line)	Human	Cytokines				Frank et al. (1998)
Pancreatic beta cells	Rat	IL-1β				Corbett et al. (1992)
Pancreatic beta cells (insulinoma RINm5F)	Rat	IL-1β	$PbCl_2$ $HgCl_2$	↑ ↓	—	Eckhardt et al. (1999)
Pancreatic beta cells (primary)	Rat	IL-1β	1. TLCK 2. MG 132	↓ ↓	Serine proteases proteosome complex	Kwon et al. (1998)
Pancreatic beta cells (insulinoma RINm5F)	Rat	IL-1β			$p38^{MAPK}$, ERK1/2	Larsen et al. (1998)
Pancreatic beta cells (primary) insulinoma RINm5F	Rat	IL-1β	1. Aspirin	↓		Kwon et al. (1997)

(*Table continues on next page*)

TABLE 1. NO Production in Different Cell Types from Different Species and Agents Used for Studying Regulation (*Continued*)

Cell type	Species	Stimulus	Agent	Effect on NO	Intracellular mechanism	Reference
Gastrointestinal						
Epithelial (intestinal) (DLD-1)	Human	IFN-γ TNF/IL-1	1. Tyrphostins 2. Calculin A 3. Okadaic acid 4. Phenylarsine oxide 5. Anisomycin	↓ ↓ ↓ ↓ ↓	JAK-2	Kleinert et al. (1998)
Epithelial (intestinal) (DLD-1)	Human	IL-1β/IFN-γ	1. Ursodeoxycholate	↓		Invernizzi et al. (1997)
Epithelial cells (colon: Caco-27 HT-29)	Human					Witthoft et al. (1998)
Epithelial cells (colon)	Human	TNF/IL-1α TNF	1. IL-13 2. IL-4 3. IL-10	↓ ↓ ↔		Kolios et al. (1998)
Kupffer cells	Rat	LPS	1. Forskolin 2. Dibutyryl cAMP 3. Cholera toxin 4. Isoproterenol	↓ ↓ ↓ ↓	cAMP	Mustafa and Olson (1998)
Hepatocytes	Rat	LPS/cytokines				Wang et al. (1998), Wood et al. (1993), Curran et al. (1989)
Hepatocytes	Human	LPS/IFN-γ TNF/IL-1				Nussler et al. (1992)
Hepatocytes	Rat	LPS/IFN-γ TNF/IL-1	1. Cycloheximide 2. Dexamethasone	↓ ↓		Geller et al. (1993)
Hepatocytes (fetal)	Rat	1. LPS 2. Cytokines	1. Cycloheximide 2. Cycloheximide	↓ ↑		Casado et al. (1997)

Hepatocytes	Rat	IL-1β	Na salicylate	↓		Sakitani et al. (1997)
Hepatocytes	1. Human 2. Mouse 3. Rat	LPS Cytokines Cytokines	EGF EGF EGF	↓ ↓ ↔		Nussler et al. (1995)
Hematologic						
B-cell chronic lymphocytic leukemia	Human					Zhao et al. (1998)
Hairy-cell leukemia	Human					Eigler et al. (1998)
HL-60 cells	Human					Kawase et al. (1998)
Macrophage (alveolar)	Rat	LPS	Lung surfactant	↓		Miles et al. (1999)
Macrophage	Mouse	IFN-γ/LPS	Cadmium	↓		Kim et al. (1998)
Macrophage	Mouse	LPS	Melatonin	↓		Gilad et al. (1998)
Macrophage	Rat	PMA	1. CRP 2. D609	↑ ↓	 PC-PLC	Ratnam and Mookerjea (1998)
Macrophage	Rat	IFN-γ/TNF/IL-1	Pentoxifylline	↓		Trajkovic et al. (1997)
Macrophage	Human	CD23	IL-10	↓		Dugas et al. (1998)
Macrophage	Human	1. Poly I:C 2. Poly I:C	 IFN-γ or α	 ↑		Snell et al. (1997)
Macrophage	Mouse	IFN-γ	Maleylated BSA	↑	—	Alford et al. (1998)
Macrophage (bone marrow)	Mouse	IFN-γ/TNF	IL-10	↑		Corradin et al. (1993)
Macrophage (bone marrow)	Mouse		Hemin	↓		Turcanu et al. (1998)
Macrophage (bone marrow)	Mouse	LPS	ANP	↓		Kiemer and Vollmar (1998)
Macrophage (peritoneal)	Mouse	IFN-γ/LPS	Modified BSA	↑		Rojas et al. (1996)

(*Table continues on next page*)

TABLE 1. NO Production in Different Cell Types from Different Species and Agents Used for Studying Regulation (*Continued*)

Cell type	Species	Stimulus	Agent	Effect on NO	Intracellular mechanism	Reference
Macrophage (peritoneal)	Mouse	LPS	IL-11	↓		Trepicchio et al. (1996)
Macrophage (peritoneal)	Mouse	IFN-γ/LPS	IFN-α/β	↓		Lopez-Collazo et al. (1998)
Macrophage (peritoneal)	Mouse	IFN-γ	TGF-β	↓		Vodovotz et al. (1993) Gilbert and Herschman (1993)
Macrophage (peritoneal) or RAW 264.7	Mouse	LPS or IFN-γ or LPS/IFN-γ	1. VIP 2. PACAP	↓ ↓		Delgado et al. (1999)
Monocyte (ANA-1)	Rat		Bryostatin+ IFN-γ	↑	PKC	Taylor et al. (1997)
Monocyte (J774)	Mouse	LPS	1. PGE2 2. Iloprost	↓ ↓		D'Acquisto et al. (1998)
Monocyte (J774)	Mouse	LPS	UTP	↑	CaMK	B.-C. Chen et al. (1998)
Monocyte (J774)	Mouse	LPS	IL-10	↓	—	Jacobs et al. (1998)
Monocyte (J774)	Mouse	LPS	Cycloheximide	↓		Hattori et al. (1996)
Monocyte (RAW 264.7 and J774)	Mouse	LPS	Melatonin	↓		Gilad et al. (1998)
Monocyte (J774)	Mouse	LPS/IFN-γ	MCP-1	↓		Rojas et al. (1993)

Monocyte (J774)	Mouse	1. LPS 2. LPS/IFN-γ	Cycloheximide Cycloheximide	↓ ↔↓		Baydoun et al. (1993)
Monocyte (J774)	Mouse	LPS	1. Indomethacin 2. PGE2 (low) 3. PGE2 (high)	↓ ↑ ↓		Milano et al. (1995)
Monocyte (RAW 264.7)	Mouse	IFN-γ/LPS	ACA	↓	IκB	Ohata et al. (1998)
Monocyte (RAW 264.7)	Mouse	IFN-γ	Dexamethasone	↓		Walker et al. (1997)
Monocyte (RAW 264.7)	Mouse	IFN-γ/LPS	PPARγ agonists	↓		Colville-Nash et al. (1998)
Monocyte (RAW 264.7)	Mouse	LPS	1. LY294002 2. Wortmannin	↑ ↑	PI3-kinase	Diaz-Guerra et al. (1999)
Monocyte (RAW 264.7)	Mouse	LPS	1. LY294002 2. Wortmannin	↓ ↔	PI3-kinase	Salh et al. (1998)
Monocyte (RAW 264.7)	Mouse	1. NC MTP Chol 2. MDP	1. TGF-β 2. IL-10 1. TGF-β 2. IL-10	↓ ↓ ↔ ↓		Seyler et al. (1997)
Monocyte (RAW 264.7)	Mouse	IFN-γ/LPS	1. Calyculin A 2. Microcystin 3. Okadaic acid 4. Cantharidin	↓ ↓ ↓ ↓	Protein phosphatase 1/2A	Pahan et al. (1998)
Monocyte (RAW 264.7)	Mouse	IFN-γ	1. $PbCl_2$	↓		Kanematsu et al. (1996)
Monocyte (RAW 264.7)	Mouse	IFN-γ/LPS	1. SB203580 2. PD98059	↓ ↓	$p38^{MAPK}$ ERK	Ajizian et al. (1999)

(*Table continues on next page*)

TABLE 1. NO Production in Different Cell Types from Different Species and Agents Used for Studying Regulation (*Continued*)

Cell type	Species	Stimulus	Agent	Effect on NO	Intracellular mechanism	Reference
Monocyte (RAW264.7)	Mouse	1. IFN-γ 2. LPS	1. IL-10 2. Pentoxifylline	↔ or ↑ ↓	— Phosphodiesterases	Loftis et al. (1997)
Monocyte (RAW264.7)	Mouse	IFN-γ LPS	1. Poly I-C 2. Poly I-C	↑ ↔		Heitmeier et al. (1998)
Monocyte (RAW 264.7)	Mouse	LPS	1. Adenosine	↑		Hon et al. (1997)
Monocyte (RAW264.7)	Mouse	LPS	1. SB203580 2. PD98059	↓ ↔	$p38^{MAPK}$ ERK	Chen and Wang (1999)
Megakaryoblastic	Human	IL-1β				Lelchuck et al. (1992)
NK cells	Human					Salvucci et al. (1998)
Polymorphonuclear leukocytes	Human					Amin et al. (1995), Miles et al. (1995), Evans et al. (1996), Malawista et al. (1992)
Polymorphonuclear leukocytes	Rat					Schafer et al. (1999)
Polymorphonuclear leukocytes	Human	LTB4, LTC4, or LTD4		↑		Lafars et al. (1999)
Polymorphonuclear leukocytes	Rat	LPS (in vivo)	1. Dexamethasone	↓		Fierro et al. (1999)
Musculoskeletal						
Cardiac myocytes	Rat	IL-1β	1. SB205380 2. PD98059	↓ ↓	$p38^{MAPK}$ $p42/44^{MAPK}$	LaPointe and Isenovic (1999)
Chondrocytes	Human	IL-1β				Palmer et al. (1993)

Chondrocytes	Human	IL-17	Dexamethasone	↓		Shalom-Barak et al. (1998)
Chondrocytes	Human					Charles et al. (1993)
Osteoblasts (primary)	Rat					Hukkanen et al. (1995)
Osteoblastic cell lines ROS 17/2.8 MC3T3-E1 MG63						
Osteoclastic cell line	Avian	LPS/IL-1α/ TNF/IFN-γ	1. Dexamethasone 2. TGF-β	↓ ↓		Sunyer et al. (1996)
Skeletal muscle (L6)	Rat	IL-1β/ IFN-γ	1. Herbimycin A 2. Genistein 3. Forskolin 4. PMA	↓ ↓ ↑ ↑	Tyrosine kinases Tyrosine kinases PKA PKC	Okuda et al. (1997)
Neural						
Astrocytes	Rat	LPS/cytokines	$LiCl_2$	↑	—	Feinstein (1998)
Astrocytes	Human	IFN-γ/IL-1β				Ding and Merrill (1997)
Astrocytes	Mouse	IL-1α/TNF	1. FHPI 2. PD98059	↓ ↔	$p38^{MAPK}$ ERK	DaSilva et al. (1997)
Astrocytes	Rat	LPS	1. Genistein 2. D609 3. Propranolol 4. U73122 5. Staurosporine 6. RO 31-8220 7. Go 6976 8. Calphostin	↓ ↓ ↓ ↔ ↓ ↓ ↓ ↓	Tyrosine kinase PC-PLC PP PI-PLC PKC PKC PKC PKC	Chen et al. (1998a)
Astrocytes	Rat	Cytokines	1. Calyculin A	↑	Protein phosphatase 1/2A	Pahan et al. (1948)
Astrocytes	Rat	IFN-γ/IL-1/TNF	Pentoxifylline	↑		Trajkovic et al. (1997)

(*Table continues on next page*)

TABLE 1. NO Production in Different Cell Types from Different Species and Agents Used for Studying Regulation (*Continued*)

Cell type	Species	Stimulus	Agent	Effect on NO	Intracellular mechanism	Reference
Glial cells (primary)	Rat	IFN-γ/LPS/TNF	Endothelin Endothelin (24 h preincub.)	↓ ↑		Murayama et al. (1998)
Glial cells (primary)	Mouse	LPS	1. IL-10 2. TGF-β	↓ ↓		Lodge and Sriram (1996)
Glial cells (fetal)	Human	IL-1β/IFN-γ				Ding et al. (1997)
Glioma cells (C6)	Rat	LPS	2. Microcystin 3. Okadaic acid 4. Cantharidin	↑ ↑ ↑		Pahan et al. (1998)
Glioma cells (C6)	Rat	IFN-γ/TNF	1. DOI (Serotonin agonist)	↓	PKC	Miller and Gonzalez (1998)
Glioma cells (C6)	Rat	IFN-γ/LPS/TNF	1. Taurine chloramine	↓	—	Liu et al. (1998)
Glioma cells (C6)	Rat	IFN-γ/IL-1β	Idazoxan	↓	—	Feinstein et al. (1999)
Neuronal (PC12)	Rat	LPS/TNF				Heneka et al. (1998)
Neuroblastoma (NB-39-nu)	Human	IFN-γ/TNF				Ogura and Esumi (1996)
Oligodendrocyte (CG4)	Rat	IFN-γ/TNF/IL-1	SB203580	↓	$p38^{MAPK}$	Bhat et al. (1999)
Renal Mesangial cells	Rat	LPS/IL-1β	1. Vasopressin 2. PDTC 3. Dexamethasone	↓ ↓ ↓	PKC	Umino et al. (1999)

Mesangial cells	Rat	1. IL-1β 2. cAMP				Eberhardt et al. (1998)
Mesangial cells	Human	IL-1β/IFN-γ				Nicolson et al. (1993)
Mesangial cells	Rat	IL-1β	Dexamethasone	↓		Kunz et al. (1996)
Mesangial cells	Rat	IL-1/TNF				Pfeilschifter and Schwazenback (1990), Shultz et al. (1991)
MTAL cells (ST-1)	Mouse	LPS/IFN-γ				Gupta and Kone (1999)
Mesangial cells	Rat	TNF/IFN-γ or LPS/IFN-γ	1. PDTC 2. NAC 3. Dexamethasone 4. Herbimycin 5. AG490 6. Anti-sense JAK-2	↓ ↓ ↓ ↓ ↓ ↓	 JAK-2 JAK-2	Nakashima et al. (1999)
Mesangial cells	Human	LPS/cytokines	IL-13	↓		Saura et al. (1996)
Mesangial cells	Rat	IL-1β	1. Angiotensin II 2. TGF-β	↓ ↓		Kihara et al. (1999)
Renal tubule cells	Rat	TNF/IFN-γ				Markewitz et al (1993)
Reproductive						
Sertoli cells	Rat	IFN-γ/TNF	1. IL-1α 2. FGF 3. TGF-β 4. dbcAMP	↔ ↑ ↔ ↑		Bauche et al. (1998)
Breast cancer cells (ZR-75-1)	Human	PMA	Tamoxifen	↓		Alalami and Martin (1998)
Epididymal	Rat	LPS/IFN-γ				Wiszniewska et al. (1997)

(*Table continues on next page*)

TABLE 1. NO Production in Different Cell Types from Different Species and Agents Used for Studying Regulation (*Continued*)

Cell type	Species	Stimulus	Agent	Effect on NO	Intracellular mechanism	Reference
Granulosa cells (ovary)	Rat	IFN-γ/IL-1β/TNF				Matsumi et al. (1998)
Leydig cells	Rat	IL-1β				Tatsumi et al. (1997)
Peritubular cells (testis)	Rat	IFN-γ/TNF	1. IL-1α 2. FGF 3. TGFβ	↔ ↔ ↓		Bauche et al. (1998)
Sertoli cells	Rat	IFN-γ/TNF	1. IL-1α 2. FGF 3. TGFβ 4. dbcAMP	↔ ↑ ↔ ↑		Bauche et al. (1998)
Leydig cells	Rat	IL-1β				Tatsumi et al. (1997)
Endometrium	Human					Tschugguel et al. (1999), Telfer et al. (1997)
Respiratory						
Epithelial (L2) (alveolar type 2)	Rat	LPS/cytokines				Hoffmann et al. (1995), Su et al. (1996)
Epithelial (L2) (alveolar type 2)	Rat	IFN-γ/TNF	G-CSF	↓	—	Hoffmann and Schobersberger (1998)
Epithelial A549 (alveolar type 2), BEAS 2B (bronchial), primary bronchial	Human	LPS/cytokines				Asano et al. (1994), Robbins et al. (1994)

Epithelial A549 (alveolar type 2)	Human	IL-1β/TNF IFN-γ	1. IL-13 2. IL-4	↓ ↓		Berkman et al. (1996)
Lung epithelial (E10 and E9)	Mouse	IL-1/TNF/IFN-γ	Dexamethasone	↓		Thompson et al. (1998)
Mesothelial cells (pleural)	Rat	IL-1/IFN-γ/LPS/TNF				(Choe et al. (1998), Owens and Grisham (1993)
Sensory						
Endothelial cells (corneal)	Bovine	IFN-γ/LPS/TNF	1. Cycloheximide 2. TGF-β 3. FGF-2	↓ ↑ ↓	— — —	Dighiero et al. (1997)
Epithelial (retinal pigmented)	Bovine	IFN-γ/LPS	1. PDTC 2. SB203580 3. PD98059 4. Genistein	↓ ↓ ↓ ↓	— $p38^{MAPK}$ ERK Tyrosine kinase	Faure et al. (1999)
Epithelial (retinal pigmented)	Bovine	LPS/TNF				Goureau et al. (1992), Liversidge et al. (1994)
Epithelial (retinal pigmented)	Rat	IFN-γ/LPS				Furukawa et al. (1995)
Epithelial (retinal pigmented)	Human	IFN-γ/TNF IL-1β	1. TGF-β	↓		Kutty et al. (1995)
Epithelial (retinal pigmented)	Bovine	IFN-γ/LPS	1. Genistein 2. Herbimycin A 3. PDTC 4. Cycloheximide	↓ ↓ ↓ ↓		Faure et al. (1998)

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TABLE 1. NO Production in Different Cell Types from Different Species and Agents Used for Studying Regulation (*Continued*)

Cell type	Species	Stimulus	Agent	Effect on NO	Intracellular mechanism	Reference
Epithelial (retinal pigmented)	Mouse	IFN-γ/LPS	1. FBF 2. EGF 3. TGF-β	↑ ↑ ↓		Sparrow et al. (1994)
Vascular						
Smooth muscle cells (aortic)	Rat	LPS	Cycloheximide	↑	—	Marczin et al. (1998), Evans et al. (1994)
Smooth muscle cells	Rat	LPS	Go6976	↓	PKCα	Li et al. (1998)
Smooth muscle cells	Rat	IL-1β	1. Aspirin 2. Na salicylate	↑ ↑		Nishio and Watanabe (1998)
Smooth muscle cells (colonic)	Rat	IL-1β/TNF	TGF-β			Kuemmerle (1998)

Note. Abbreviations: ACA, 1′-acetoxychavicol acetate; ANP, atrial natriuretic peptide; CRP, C-reactive protein; D609, tricyclodecan-9-yl-xanthogenate; EGF, epidermal growth factor; FGF, fibroblast growth factor; FHPI, 4-(4-fluorophenyl)-2-2-(hydroxyphenyl)-5-(4-pyridyl)imidazole; G-CSF, granulocyte colony-stimulating factor; IL,interleukin; IFN, interferon; LPS, lipopolysaccharide; MCP-1, macrophage chemotactic peptide-1; MDP, soluble muramyl dipeptide; NAC, *N*-acetyl-L-cysteine; PACAP, pituitary adenylate cyclase-activating polypeptide; NC MTP-Chol, muramyl tripeptide cholesterol included in biodegradable poly (D,L-lactide) nanocapsules; PC-PLC, phosphatidylcholine phospholipase C; PDTC, pyrrolidine dithiocarbonate; PI3-kinase, phosphatidylinositol 3-kinase; PKA, protein kinase A; PKC, protein kinase C; PMA, β-phorbol 12-myristate 13-acetate; PPARγ, peroxisome proliferator receptor-γ; TGF, transforming growth factor; TLCK, *N*-α-P-tosyl-L-lysine chloromethyl ketone; TNF, tumor necrosis factor; UTP, uridine triphosphate; VIP, vasoactive intestinal peptide.

Xie et al., 1993), human (Chartrain et al., 1994; Zhang et al., 1996; de Vera et al., 1996; Spitsin et al., 1996; Charles et al., 1993), rat (Zhang et al., 1998; Eberhardt et al., 1996), and avian (Lin et al., 1996) promoter regions of iNOS gene. The promoters from human (Chartrain et al., 1994; Zhang et al., 1996) and mouse iNOS genes (Lowenstein et al., 1993; Xie et al., 1993) have some common elements, with a homology of 55% within the first 1.7 kb of 5′ flanking sequence (Zhang et al., 1996). Both contain consensus sequences for numerous *cis*-actin regulatory elements. The mouse iNOS gene promoter contains two regions or clusters of regulatory elements, a proximal and a distal region. The proximal region (region I or RI) extends from position –48 to –209, functions as the basal promoter element, and mediates response to lipopolysaccharide (LPS) through NF-κB and interferon response factor (IRF) binding (Xie et al., 1993; Lowenstein et al., 1993; Alley et al., 1995). The distal region (region II or RII) extends from –913 to –1029, functions as an enhancer element, and responds to LPS and interferon (IFN)-γ stimulation through NF-κB and IRF-1 binding (Lowenstein et al., 1993; Alley et al., 1995). The human iNOS gene promoter contains sequences homologous to mouse RI and RII (Chartrain et al., 1994; Zhang et al., 1996). Although the regulatory elements in RI are well conserved between mouse and human promoters, the elements in human RII are less conserved and would be predicted to be nonfunctional based upon their comparison to consensus sequences (Zhang et al., 1996).

In the mouse iNOS gene, 1000 base pairs out of the 1.5-kb mouse iNOS promoter confer full inducibility in response to a mixture of IFN-γ and LPS in a cultured mouse macrophage cell line, RAW 264.7 (Xie et al., 1993; Lowenstein et al., 1993). In the rat iNOS gene, a 3.2-kb promoter construct was required for full inducibility. In the human iNOS gene, a 3.7-kb segment of 5′-flanking region does not contain all of the elements required for transcriptional induction (Laubach et al., 1997); a full-length 16-kb promoter is required for induction by a cytokine mixture even though the full sequence and elements of this promoter are still unknown (de Vera et al., 1996). In the chicken iNOS gene, an LPS-responsive region is located exclusively within 300 base pairs upstream of the transcription initiation site (Lin et al., 1996). Thus, there are significant differences in the promoter regions of iNOS from different species.

In addition to the differences in the iNOS promoters from different species, molecular regulation of transcription appears to differ among different cell types in the same species. For example, in a mouse macrophage cell line, RAW 264.7, the promoter region that responds to LPS contains only a single downstream NF-κB binding site (Xie et al., 1994). But in the vascular smooth muscle cell line, A7r5, it is the –890 to –1002 bp region (also containing another NF-κB site) that responds better to cytokines (Spink et al., 1995). Furthermore, interspecies differences in the transcriptional regulation are demonstrated by the fact that the mouse iNOS pro-

moter is unresponsive to cytokines when transfected into human colonic epithelial cells (Laubach et al., 1997).

ROLE OF TRANSCRIPTIONAL FACTORS

The transcriptional control of iNOS gene expression in vascular smooth muscle cells has been recently reviewed (Hecker et al., 1999). Here, recent observations concerning the role of various transcription initiation factors are discussed. The promoter region of the mouse iNOS gene contains several binding sites for nuclear factor kappa B (NF-κB), activator protein 1 (AP-1), and various members of the CCAAT/enhancer binding protein (C/EBP), cAMP-responsive element-binding protein (CREB), and signal transducers and activators of transcription (STAT) family of transcription factors.

NF-κB

Activation of NF-κB has been shown to mediate enhanced expression of the iNOS gene in mouse macrophages exposed to LPS (Xie et al., 1994) and vascular smooth muscle cells (Spink et al., 1995) and mesangial cells (Eberhardt et al., 1994) exposed to interleukin-1β. However, it is unlikely to act as an important factor for cytomix-stimulated iNOS in human epithelial DLD-1 cells (Kleinert et al., 1998). NF-κB activated by LPS induces iNOS in mouse macrophages (Lorsbach et al., 1993), whereas NF-κB generated by TNF-α fails to induce iNOS in renal epithelial cells (Amoah-Apraku et al., 1995). In renal mesangial cells, iNOS was induced even after total abolishment of active NF-κB (Nakashima et al., 1999). So it seems that although NF-κB plays an important role in iNOS induction it is not essential for iNOS expression, at least in certain cell types.

AP-1

AP-1 acts as an inhibitor of iNOS gene expression in both murine macrophages (Lowenstein et al., 1993) and human epithelial DLD-1 cells (Kleinert et al., 1998). Thus, AP-1 seems to exert a negative influence on iNOS transcription. But using luciferase plasmid constructs of a human promoter, both AP-1 and NF-κB were shown to be important for induction of human iNOS gene transcription (Marks-Konczalik et al., 1998).

CREB and C/EBP

Elevated cAMP levels induce iNOS expression in rat vascular smooth muscle cells (Hecker et al., 1997), in rat macrophages *in vitro* and *in vivo* (Sowa & Przewlocki, 1995; Greenberg et al., 1997), and in rat renal mesangial cells (Eberhardt et al., 1994). cAMP acts through C/EBP family of transcription factors. But cAMP regulation of iNOS expression is unique to the rat iNOS promoter. C/EBPβ (NF-IL6) seems to be important for maintaining a high transcriptional rate of the iNOS gene after IFN-γ/LPS stimulation in J774A.1 murine macrophages (Dlaska & Weiss, 1999). NF-κB

and C/EBP also cooperate in a synergistic manner in the induction of iNOS gene expression in VSMC (Hecker et al., 1997).

ROLE OF KINASES IN iNOS TRANSCRIPTIONAL REGULATION

Various kinases have been implicated in iNOS regulation. These include (1) protein kinase C in liver cells (Chen et al., 1998a), microglial cells (Fiebich et al., 1998), vascular smooth muscle cells (Li et al., 1998), and RAW 264.7 cells (Chen et al., 1998b); (2) protein kinase A in vascular smooth muscle cells (Imai et al., 1994), microglial cells and astrocytes (Hellendall & Ting, 1997), and macrophages (Mullet et al., 1997); and (3) protein tyrosine kinases in microglial cells and astrocytes (Kong et al., 1996; Hellendall & Ting, 1997) and in liver cells (Lee et al., 1997). These kinases in turn initiate kinase cascades involving several other kinases, and some of the cellular kinases implicated in iNOS regulation are described next.

JAK-STAT Pathway

Exposure of cells to IFN-γ results in the activation of protein tyrosine kinases such as the janus kinases, JAK-1 and JAK-2, which phosphorylate and activate STAT1α. The activated STAT1α translocates into the nucleus and induces transcription of IFN-γ regulated genes (Schindler & Darnell, 1995). The IFN-γ–JAK2–STAT1α-pathway is important in iNOS induction in rodent cells (Kitamura et al., 1996; Nishiya et al., 1997; Singh et al., 1996) and in human DLD-1 cells (Kleinert et al., 1998). In renal mesangial cells, JAK2 plays an essential role in IFN-γ signal transduction, and the contribution of JAK2 to nitrite production is greater than that of NF-κB (Nakashima et al., 1999).

Mitogen-Activated Protein Kinases (MAP) Kinases

The stimulants that induce nitric oxide production are known to activate MAP kinases, which play an important role in transcription (Davis, 1994; Kyriakis & Avruch, 1996) and translation (Prichett et al., 1995). The MAP kinase group consists of three families of kinases: $p38^{MAPK}$, $p42/44^{MAPK}$ (ERK1/ERK2), and JNK/SAPK. LPS activates all three kinases in murine RAW 264.7 cells (Sanghera et al., 1996; Swantek et al., 1997). Similarly, all three MAP kinases are activated in mouse bone marrow-derived macrophages stimulated with tumor necrosis factor (TNF) alone. Further, addition of IFN-γ to TNF did not cause a significant change in activation (Chan et al., 1999). IL-1β activates $p38^{MAPK}$ and $p42/44^{MAPK}$ in cardiac myocytes (LaPointe & Isenovic, 1999). Activation of $p38^{MAPK}$ and $p42/44^{MAPK}$ also occurs in bovine retinal pigmented epithelial cells stimulated with IFN-γ and LPS (Faure et al., 1999). Larsen et al. (1998) concluded that in rat islet cells and insulinoma cells activation of $p38^{MAPK}$ and $p42/44^{MAPK}$ is necessary but not sufficient for NO production in IL-1β-stimulated cells.

Similarly, in mouse astrocytes stimulated with IL-1α and TNF-α, $p38^{MAPK}$ activation was necessary but not sufficient to transduce the signal, and inhibition of $p42/44^{MAPK}$ with PD98059 had no marked effect (Da Silva et al., 1997). In RAW 264.7 cells also stimulated with LPS, it was activation of $p38^{MAPK}$ that was found to be important in regulating iNOS induction (Chen & Wang, 1999). In another study using RAW 264.7 cells stimulated with a combination of LPS and IFN-γ, both $p42/44^{MAPK}$ and $p38^{MAPK}$ were implicated in iNOS expression (Ajizian et al., 1999). Similarly in rat microglial cells and astrocytes treated with LPS or the combination of LPS/IFN-γ, respectively, $p42/44^{MAPK}$ and $p38^{MAPK}$ were shown to cooperate in iNOS induction (Bhat et al., 1998). Yet in another study of bone marrow-derived mouse macrophages stimulated with TNF, it was reported that JNK/SAPK was involved in regulating NO production (Chan et al., 1999). The conclusions in many of these studies are based on the use of supposedly specific inhibitors of particular kinases. It is well known that over time other secondary effects of inhibitors become evident and render the interpretations based on inhibitors very tentative. For example, it has been shown recently that the $p38^{MAPK}$ inhibitor SB203580 activates the serine/threonine kinase Raf-1 in vascular smooth muscle cells (Daum et al., 1999). In addition, careful comparative studies may be required to identify how much of this variation is due to technical differences, and what role cell- and stimulus-specific differences play in these data.

Phosphatidylinositol 3-Kinase

Stimulation of RAW 264.7 cells with LPS activates phosphatidylinositol 3-kinase (PI3-kinase) and has been assigned a negative role in iNOS regulation (Diaz-Guerra et al., 1999). In fact, it appears that inhibition of PI3-kinase may be a necessary event for production of NO following stimulation in C6 glial cells and rat primary astrocytes (Pahan et al., 1999). Additional evidence for a role of PI3-kinase in NO regulation comes from the observation that inhibition of iNOS expression by activation of RON (receptor d' origine nantais) tyrosine kinase is mediated through activation of PI3-kinase (Y.-Q. Chen et al., 1998).

Protein Phosphatases

Involvement of so many kinases in iNOS regulation implies that phosphatases may also play a role in its regulation. Compounds that inhibit protein phosphatases 1 and 2A (calyculin, microcystin, okadaic acid, and cantharidin) stimulate LPS/cytokine-mediated expression of iNOS and production of NO in rat primary astrocytes and glial cells; however, the same agents inhibit the LPS/cytokine-mediated expression of iNOS and production of NO in rat resident macrophages and RAW 264.7 cells (Pahan et al., 1998). Again the actual mechanisms for these differences are not clear at the present time.

Many of these kinases play a role in the transcriptional regulation of the iNOS gene. But it is becoming clear that these kinases also play an

important role in translational regulation of genes. Recent findings indicate that translational regulation may play a crucial role in fine-tuning iNOS gene expression. The role of these kinases in such regulation is discussed later, but we next return to events following the transcription of iNOS gene.

iNOS REGULATION BY mRNA STRUCTURE

The first data suggesting that posttranscriptional mechanisms are involved in the regulation of iNOS expression were provided by Vodovotz et al. (1993). They showed that TGF-β decreases iNOS expression by decreasing iNOS mRNA stability, reducing iNOS mRNA translation, and increasing degradation of iNOS protein in mouse peritoneal macrophages. The complex effects of TGF-β in various cell types have been reviewed (Vodovotz, 1997) and are briefly described in Table 1.

There is increasing evidence that the 5′- and 3′-untranslated regions (UTRs) of many mRNAs play an important role in the regulation of gene expression by influencing mRNA stability and translational efficiency (Kozak, 1992; Altmann & Trachsel, 1993). Despite the presence of a TATA box in the promoter region, multiple transcription initiation sites have been observed in different types of human cells and human cell lines. Alternative splicing of 5′-UTR of human iNOS mRNA results in further diversity (Chu et al., 1995). The TATA-independent iNOS mRNA transcripts are upregulated by cytokines. The long and complex 5′-UTRs contain eight partially overlapping open reading frames upstream of putative inducible nitric oxide synthase ATG and have been proposed to have a role in translational regulation of human iNOS (Chu et al., 1995). In addition, the 3′-UTRs of both murine and human iNOS mRNAs have a conserved AU-rich octanucleotide sequence, which is known to mediate mRNA stability (Evans et al., 1994). There also appears to be a cooperative interaction between 5′- and 3′-UTRs in the induction of human iNOS (Nunokawa et al., 1997).

iNOS Regulation at the Translational Level

Dexamethasone (Walker et al., 1997) and IL-13 (Bogdan et al., 1997) inhibit NO production by inhibiting the translation of iNOS mRNA in certain cell types. Similarly, sodium salicylate has been shown to decrease iNOS protein levels in rat hepatocytes (Sakitani et al., 1997) and RINm5F cells and rat islet cells (Kwon et al., 1997). Maleyl-BSA (Maleyl-bovine serum albumin) is another agent that regulates iNOS expression at the translational level (Alford et al., 1998). Recently, lung surfactant has been shown to decrease iNOS protein levels without decreasing the steady-state mRNA levels (Miles et al., 1999). This decrease may also occur at a translational level. However, the mechanism of action for these agents is not known. Study of translational control of iNOS gene may contribute to our understanding of the translational regulation of gene expression in eukaryotic cells.

iNOS Regulation at the Posttranslational Level

NO production can also be modulated after the synthesis of iNOS protein by alterations in the stability of the protein. Dexamethasone decreases iNOS protein stability in IL-1β-stimulated rat renal mesangial cells (Kunz et al., 1996) and IFN-γ-stimulated RAW 264.7 cells (Walker et al., 1997). It appears that the cysteine protease calpain I may be involved in the increased degradation of the iNOS protein caused by dexamethasone. TGF-β also decreases protein stability and in addition reduces iNOS mRNA translation. Another posttranslational regulatory event is the tyrosine phosphorylation of iNOS protein, which seems to activate the enzyme (Pan et al., 1996).

AN ANALYSIS OF THE EXISTING DATA AND FUTURE DIRECTIONS

iNOS, by definition, has been known to be an enzyme that is newly synthesized following cytokine stimulation. Resting cells have no detectable message, and iNOS mRNA is newly synthesized following stimulation. Therefore, transcriptional regulation of iNOS was the focus of early investigations. The first evidence that iNOS is subject to other than transcriptional regulation was based on the effect of TGF-β on mouse peritoneal macrophages stimulated with IFN-γ (Vodovotz et al., 1993). Since then it has become clear that iNOS is regulated at various levels of synthesis and degradation as described earlier in this review. This level of complexity makes the interpretation of data difficult, and requires one to pay careful attention to the experimental conditions described. The varied effects of TGF-β, depending on the cell type, have been reviewed (Vodovotz, 1997) and can be rapidly perused in Table 1. In addition, it has been shown that the same agent under different incubation conditions produces different effects. For example, when endothelin is added to glial cells together with cytokines, it enhances iNOS production. When it is added 24 h before cytokines, endothelin suppresses NO production (Murayama et al., 1998). Cycloheximide suppresses NO production in hepatocytes stimulated with LPS and enhances NO mRNA in cells treated with cytokines (Casado et al., 1997). Epidermal growth factor decreases NO production in LPS-stimulated human hepatocytes and cytokine-stimulated mouse hepatocytes, but has no marked effect on cytokine-stimulated rat hepatocytes (Nussler et al., 1995). These few examples suffice to show the complexity of the phenomenon regulating NO production in mammalian cells. This poses a great challenge, and at the same time offers a great opportunity to understand gene regulation in mammalian cells.

A number of kinases have been implicated in iNOS regulation as described earlier. As reflected in the studies involving MAP kinases, conflicting data exist with regard to their role in iNOS regulation. Part of these differences may well be due to different cell types being studied; one would expect that the complex maze of signal transduction networks

works differently in different cell types. In fact, signal transduction pathways differ in the same cell type, depending upon the stage of maturation (Lucas et al., 1998). But in many cases the conclusions are based on supposedly specific inhibitors. The specificity of the inhibitors is always subject to revision and should be regarded with caution. More reliable are the studies using molecular biology techniques such as antisense oligonucleotides (Nakashima et al., 1999; Chen et al., 1998b), expression of dominant-inhibitory proteins (Y.-Q. Chen et al., 1998; Nishiya et al., 1997; Swantek et al., 1997; Hu et al., 1998), or gene knockout animals (Ambs et al., 1998; Shull et al., 1992; Vodovotz et al., 1996).

In view of the fact that 5′- and 3′-UTR play an important role in regulating the ultimate production of NO, studies using expression vectors containing only promoter regions may not yield the true picture of NO production. Expression vectors containing full-length cDNAs with a full complement of 5′- and 3′-UTRs may be necessary to understand the complexities of iNOS regulation.

MAP kinases have been recognized generally for their role in mediating signal transduction events regulating transcription, but recent studies implicate them in the regulation of translational events also. The eukaryotic initiation factor eIF4E is phosphorylated by MAP kinases. Specifically, the $p38^{MAPK}$ inhibitor SB203580 blocks the phosphorylation of eIF4E (X. Wang et al., 1998). Treatment with SB203580 has been shown to inhibit NO production in many cell types, using a variety of stimuli (see Table 1). It remains to be clarified what role the effects on transcription and translation play in inhibition of NO caused by this agent. Such studies might be very useful in understanding the translational regulation of gene expression. In this regard it is important to note that two other proinflammatory molecules, TNF (Prichett et al., 1995) and IL-β (Kaspar & Gehrke, 1994), are also under translational regulation, in addition to other types of regulation. It would be interesting to see if translational regulation of all three proinflammatory molecules share a similar mechanism.

At first sight, as Table 1 indicates, interpretation of data is complicated by differences in the types of cells studied, by the variety of stimulants used, and by the contradictory effect of various inhibitors. The challenge facing the investigators in the field is to delineate how many of the contradictions are due to experimental artifacts and what constitutes real physiologic variation. If this challenge can be met successfully, the study of iNOS regulation may provide important information on various ways gene expression may be regulated in eukaryotic cells and the various signal transduction events that may be involved in different cell types.

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