
BIOGRAPHICAL SKETCH

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NAME Jyoti J. Watters	POSITION TITLE Associate Professor		
eRA COMMONS USER NAME			
EDUCATION/TRAINING (<i>Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.</i>)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
University of Arizona, Tucson	B.S.	1986-1990	Microbiol/Immunology
University of Washington, Seattle	Ph.D.	1992-1997	Pharmacology
University of Wisconsin, Madison	Post-doc	1998-2002	Biochem./Biomol. Chem

A. Personal Statement

The overall goal of my research program is to investigate the molecular mechanisms whereby hypoxia and purinergic receptors regulate microglial gene expression. We have found that tissue oxygen history influences purinergic receptor activity such that P2X receptor activation has opposite effects depending on whether reoxygenation has occurred. Ours are the first studies to show that hypoxia/reoxygenation induces inflammatory gene expression in microglia, an effect that coincides with a reversal in the dominant P2X receptor subtype in microglia (from P2X7 to P2X4). I have a broad background in neuroimmunology and pharmacology with specific training and expertise in key research areas fundamental to this application. During my PhD work, I was trained in one of the top signal transduction/pharmacology departments in the country, and my direct mentors were Nobel Laureates and other pioneers in the field of neuroscience. During my postdoctoral work, I expanded my signal transduction and gene expression studies into the fields of immunology and purinergic receptors in macrophages, under the guidance of equally esteemed mentors. As a faculty member, I merged my training in neuroscience and immunology in the study of signaling and regulation of inflammatory gene expression following purinergic receptor activation in microglia. I laid the groundwork for our present research in previous studies by identifying key purinergic receptors, signal transduction pathways and transcription factors that have the capacity to regulate the balance of microglial neurotoxic and neurotrophic gene expression in different oxygen conditions. Given the significance of cognitive impairment resulting from intermittent hypoxia both in adult and pediatric populations, current studies are aimed at extending these concepts from microglial cell lines and neonatal primary microglial cultures to primary microglial cultures from older/adult animals, and to microglia freshly-isolated *ex vivo* from the cortex and hippocampus of animals exposed to single and multiple bouts of hypoxia reoxygenation (i.e. chronic intermittent hypoxia). Neurons in these CNS regions are most sensitive to intermittent hypoxia. The effects of intermittent hypoxia on microglial activities and their contributions to functional CNS deficits have not been previously addressed. To successfully perform the proposed studies, we have developed novel tools with which to study microglial responses to hypoxia/reoxygenation *in vitro* and *in vivo*. In this regard, we have several papers already published or submitted, and others are in preparation using these techniques. I actively train graduate, post-doctoral and undergraduate students, and my collaborations with other researchers have produced several high quality peer-reviewed publications; we fully expect this trend to continue. Our experience and background with this system, coupled with the novel methodologies we have developed to study older/adult microglia *in vitro* and *in vivo* at the molecular and biochemical levels is ideal for the proposed studies.

B. Positions and Honors

Positions and Employment

1990-1992 Research Technologist, University of Washington, Veteran's Administration Hospital
1992-1997 Graduate Student, University of Washington, Seattle with Dr. Daniel M. Dorsa

- 1998-2001 Post-Doctoral Associate, Department of Biochemistry, University of Wisconsin, Madison with Dr. Jack Gorski
- 1999-2002 NIH Post-Doctoral Fellow (8/99-7/01), Department of Biomolecular Chemistry, University of Wisconsin, Madison with Dr. Paul J. Bertics
- 2002-2009 Assistant Professor, Department of Comparative Biosciences, School of Veterinary Medicine, University of Wisconsin
- 2002-present Center for Women's Health Research, University of Wisconsin
- 2002-present Faculty member, Endocrine and Reproductive Physiology Program, Neuroscience Training Program, Comparative Biomedical Sciences Training Program, Program in Cellular and Molecular Biology, University of Wisconsin
- 2003-present Faculty member, University of Wisconsin Comprehensive Cancer Center
- 2009-present Associate Professor, Department of Comparative Biosciences, School of Veterinary Medicine, University of Wisconsin

Professional Memberships

- 1993 American Association for the Advancement of Science
- 1994 Society for Neuroscience
- 1998 Endocrine Society
- 2001 Women in Endocrinology, Women in Neuroscience
- 2005 American Society for Neurochemistry

Honors and Awards

- Honors B.S. Cum Laude, University of Arizona, 1990
- NIH Predoctoral Trainee, University of Washington, 1993-1996
- Endocrine Society Travel Award 1999, 2002
- Women in Endocrinology Travel Award 2002
- NIH Postdoctoral Fellow, (NRSA, National Cancer Institute) University of Wisconsin 8/99-7/01
- New investigator award Society for Women's Health Research Conference 2000-2003
- Inaugurated into the International Biography Center, Cambridge, England 2006
- Inaugurated into Who's Who Among Executives and Professionals, Honors Edition 2008
- Standing member of editorial board for "Inflammation and Allergy- Drug Targets" 2008-2011

C. Selected peer-reviewed publications (in chronological order) (Total publications=34)

Watters, J.J., Campbell, J.S., Cunningham, M.J., Krebs, E.G. and Dorsa, D.M. 1997 Rapid membrane effects of steroids in neuroblastoma cells: Effects of estrogen on mitogen activated protein kinase signaling cascade and c-fos immediate early gene transcription. Endocrinology 138(9): 4030-4033. (PMID: 9275096)

Watters, J.J. and Dorsa, D.M. 1998 Transcriptional effects of estrogen on neurotensin gene expression involve cAMP/protein kinase A-dependent signaling mechanisms. J. Neuroscience 18(17): 6672-6680. (PMID: 9712639)

Watters, J.J., Chun, T.Y., Kim, Y.N., Bertics, P.J. and Gorski, J. 2000 Estrogen modulation of prolactin gene expression requires an intact mitogen activated protein kinase signal transduction pathway in cultured rat pituitary cells. Molecular Endocrinology 14(11): 1872-1881. (PMID: 11075818)

Watters, J.J., Sommer, J.A., Denlinger, L.C., Pfeiffer, Z.A., Guerra, A.N., Aga, M., Proctor R.A. and Bertics, P.J. 2001 P2X₇ Nucleotide Receptors: Implications for Involvement in LPS-Induced Macrophage Signaling and Function. Drug Development Research 53: 91-104.

Watters, J.J., Sommer, J.A., Pfeiffer, Z.A., Guerra, A.N., Prabhu, U. and Bertics, P.J. 2002 LPS potently induces nitric oxide and interleukin-1 β production but fails to activate ERK-1 and ERK-2 in murine microglial cells. J. Biological Chemistry 277:9077-9087. (PMID: 11786532)

Aga, M.* and **Watters, J.J.***, Pfeiffer, Z.A., Wiepz, G.J., Sommer, J.A. and Bertics, P.J. 2004 Evidence for nucleotide receptor modulation of the cross-talk between MAP kinase and NF- κ B signaling pathways in murine RAW 264.7 macrophages. Am. J. Physiology, 286: C923-C930. * both contributed equally. (PMID: 14684387)

Baker-Herman, T.L., Fuller, D.D., Bavis, R.W., Zabka, A.G., Golder, F.J., Doperalski, N.J., Johnson, R.A., **Watters, J.J.** and Mitchell, G.S. 2004 BDNF is necessary and sufficient for spinal respiratory plasticity following intermittent hypoxia. Nature Neuroscience, 7(1):48-55. (PMID: 14699417)

Baker, A. E. Brautigam, V., and **Watters, J.J.** 2004 The anti-inflammatory effects of estrogen in murine BV-2 microglia are mediated by estrogen receptor β . Endocrinology. 145(11):5021-5032. (PMID: 15256495)

Brautigam, V.M., Frasier, C., Nikodemova, M. and **Watters, J.J.** 2005 Purinergic Receptor Modulation of Microglial Cell Activity: Potential Involvement of p38 MAP Kinase and CREB. J. Neuroimmunol, (166)113-125. (PMID: 15979729)

Nikodemova, M., Duncan, I.D. and **Watters, J.J.** 2006 Minocycline exerts inhibitory effects on multiple members of the mitogen-activated protein kinases in a stimulus specific manner in microglia in vitro. J. Neurochemistry, 96:314-323. (PMID: 16336636)

Potucek, Y.D., Crain, J.M. and **Watters, J.J.** 2006 Purinergic receptors modulate MAP kinases and transcription factors that control microglial inflammatory gene expression. Neurochem. International, 49:204-214. (PMID: 16735081)

Nikodemova, M., **Watters, J.J.**, Jackson, S.J., Young, S.K. and Duncan, I.D. 2007 Minocycline downregulates MHC II expression in microglia and macrophages through inhibition of IRF-1 and PKC α/β II. J. Biol. Chem., 282(20):15208-15216. (PMID: 17395590)

Brautigam, V.M., Dubyak, G.R., Crain, J.M. and **Watters, J.J.** 2008 Inflammatory effects of UDP-glucose in N9 microglia are independent of P2Y₁₄ Receptors. Purinergic Signaling, 4:73-78. (PMCID: PMC2246002)

Crain, J.M., Nikodemova, M. and **Watters, J.J.** 2009 Purinergic receptor expression varies with age and sex in freshly isolated brain microglia. J. Neuroinflammation, 6:24. (PMCID: PMC2744668).

Friedle, S.A., Nikodemova, M., Wright, M.L. and **Watters, J.J.** 2010 The P2X7-Egr Pathway Regulates Nucleotide-Dependent Inflammatory Gene Expression in Microglia. Glia. In press. (NIHMS# 228326)

D. Research Support

Ongoing Research Support

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