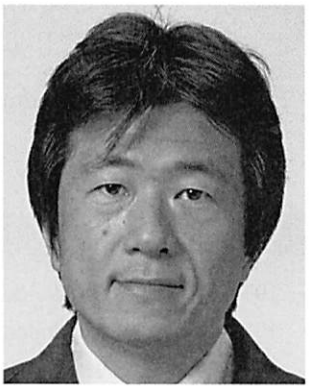
Functional Analyses of PYNOD (NLRP10) in Mice



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Many members of the nucleotide-binding and oligomerization domain (NOD) and leucine-rich-repeat (LRR)-containing protein (NLR) family play important roles in pathogen recognition and inflammation. We identified PYNOD/NLRP10, one of the member of this family that lacks LRR, and found that human and mouse PYNOD inhibits inflammatory signal mediated by caspase-1 and ASC using HEK293-based reconstitution system and PYNOD-transgenic mice.

To further investigate physiological function of PYNOD, we have established PYNOD-deficient mice. PYNOD-deficient mice exhibited no obvious gross abnormalities and no evidence of autoimmunity and spontaneous tumor formation. Macrophages from PYNOD-deficient mice produced normal level of inflammatory cytokines (IL-1β, IL-6, and TNFα) after bacterial and viral infection that we tested. In addition, there was no difference in the susceptibility of wild-type and PYNOD-deficient mice to LPS-induced endotoxin shock. Although, physiological role of PYNOD in innate immune system is still unclear, we found that PYNOD-deficient mice exhibit severe defect of delayed-type hyper sensitivity (DTH) response. This result indicates that PYNOD play important roles in acquired immune system.

Interestingly, we have found that PYNOD and caspase-1 is highly expressed in stomach of gastric cancer mouse model (*Gan* mice), in which inflammatory COX-2/PGE_2 pathway and Wnt signaling are activated simultaneously in gastric mucosa. Furthermore, we also detected high PYNOD expression in gastric cancer of human patient. We are currently trying to establish Gan-PYNOD-deficient mice to investigate PYNOD function during inflammation and tumorigenesis.

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EDUCATIONS/TRAINING

1989	Kumamoto University School of Medicine, Japan (MD)
1993	PhD from Kumamoto University, Japan

POSITIONS AND HONORS

1993-1994	Medical staff, Kumamoto university hospital, Japan
1994-1998	Postdoctoral fellow, DNAX Research Institute, USA
1998-present	Assistant professor, Division of Immunology and Molecular Biology, Cancer Research Institute, Kanazawa Univ., Japan

RECENT PUBLICATIONS

1. N. Harashima, T. Inao, R. Imamura, S. Okano, T. Suda, and M. Harada: Roles of the PI3K/Akt pathway and autophagy in TLR3 signaling-induced apoptosis and growth arrest of human prostate cancer cells. ***Cancer Immunol Immunother*** 61:667-676 (2012)
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3. R. Imamura, Y. Wang, T. Kinoshita, M. Suzuki, T. Noda, J. Sagara, S. Taniguchi, H. Okamoto, and T. Suda: Anti-inflammatory activity of PYNOD and its mechanism in human and mice. ***J. Immunol***. 184: 5874-5884 (2010)
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5. M. Hasegawa, R. Imamura, K. Motani, T. Nishiuchi, N. Matsumoto, T. Kinoshita, and T. Suda: Mechanism and repertoire of apoptosis-associated speck-like protein containing a caspase recruitment domain-mediated gene expression. ***J. Immunol***. 182:7655-7662 (2009)
6. N. Matsumoto, R. Imamura, and T. Suda: Caspase-8- and JNK-dependent AP-1 activation is required for Fas ligand-induced IL-8 production. ***FEBS Journal***. 274: 2376-2384 (2007)
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8. M. Hasegawa, K. Kawase, N. Inohara, R. Imamura, WC. Yeh, T. Kinoshita, and T. Suda: Mechanism of ASC-mediated apoptosis: Bid-dependent apoptosis in type II cells. ***Oncogene*** 26:1748-1756, (2006)