

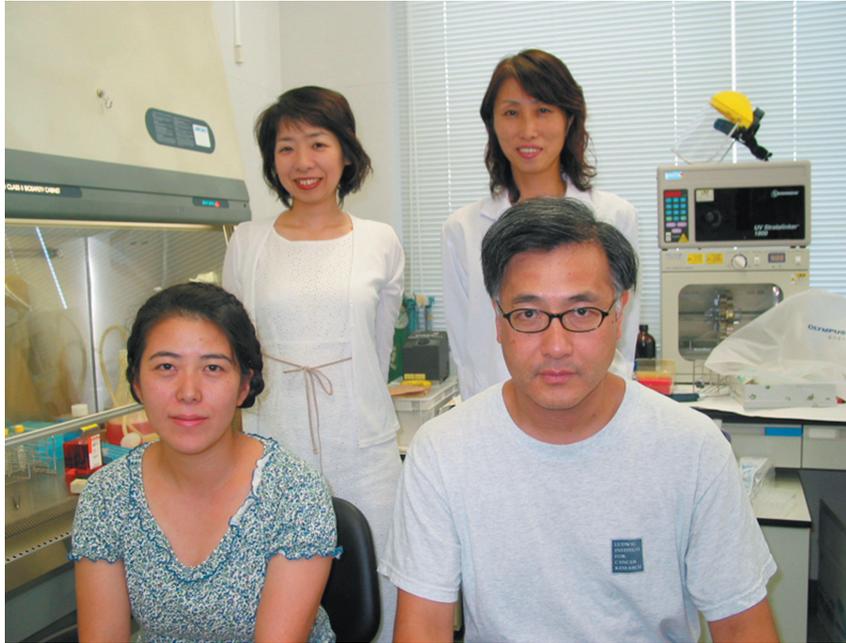
Technology and Development Team for BioSignal Program

Subteam for BioSignal Integration

Takahiro DOI

Subteam Leader, Subteam for BioSignal Integration

Goal	<p>Lives always receive stimulation from outside and maintain themselves in response to such stimulation through the complex network of signal transduction. Analysis of this mechanism is the way to elucidate bio response mechanism and to characterize bioresource materials. The main goal of our subteam is to develop new techniques for elucidation of signal transduction mechanism on bio response through the analysis of gene and protein expression using microchip array technique and database at each step including genes, cells, tissues and whole bodies. And the other goal is elucidation of the effect toward lives by abnormal cytokine networks and the mechanisms of diseases including cancers through analysis of signal transduction pathways of cytokines. Furthermore it's the another goal of ours is to develop the model mice for human diseases with the reconstruction of abnormal networks in vivo in the base of the bioinformation stored in BRC for the more detailed study and development of the new treatment for those diseases.</p>
Activities	<ol style="list-style-type: none">1. Analysis of signal transduction pathways and network in bioresponse.2. Elucidation of the mechanism of tumorigenesis based on the analysis of transcription factors and suppressor oncogenes.3. Characterization of bioresource with expression profiling.4. Development of the new technique for high throughput analysis of genes and protein.5. Construction of database and network linkage system of information.6. Development of the new technique for analysis of gene function in vivo.7. Development of the model mice for human diseases.
Members	<p>Subteam Leader, Subteam for BioSignal Integration Takahiro DOI, Ph. D. (2002. 1 ~)</p> <p>Research & Development Scientist Setsuko MISE, Ph. D. (2002. 9 ~)</p> <p>Technical Staff Noriko UCHIYAMA (2002. 5 ~)</p> <p>Assistant Michie ITOH (2002. 5 ~)</p>



Itoh, Uchiyama,
Mise, Doi

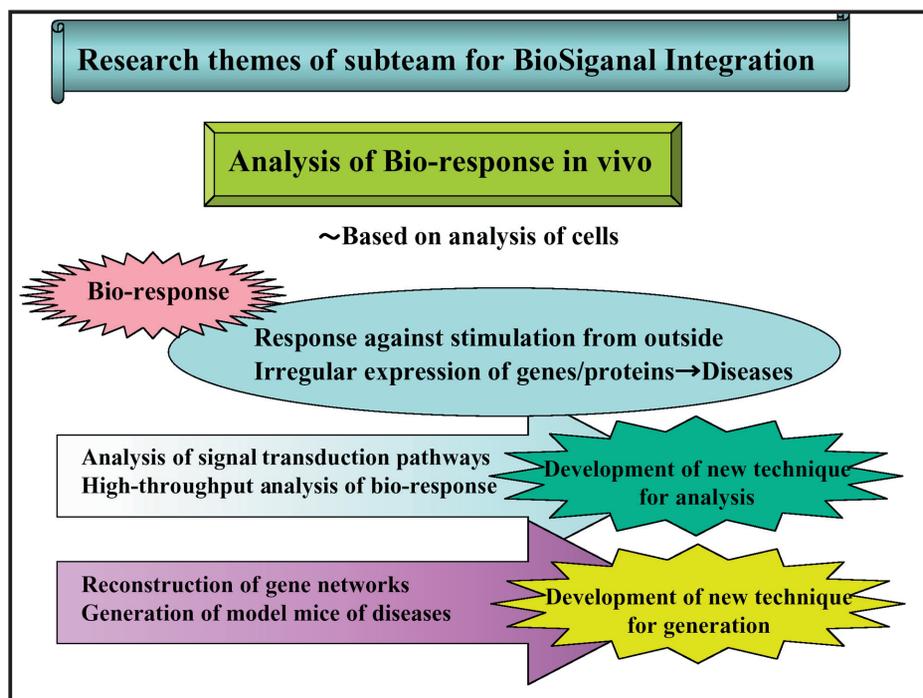


Figure 1.
Development of the new technique for analysis of bioresponse in vivo and generation of model mice.

Specific aim

I.

1. Analysis of signal transduction programs and network mechanism of cytokines (TNF, TGF- β and IFN- γ).
2. Analysis of mechanism of tumorigenesis with the major transcription factors (NF- κ B and AP-1).
3. Characterization of various biological resources collected in RIKEN BRC by analysis of expression profiles of genes and proteins.
4. Development of the available model mice for human diseases.

II.

1. Development of the high-throughput analysis system at each level from genes to whole bodies of various biological resources collected in RIKEN BRC
2. Development of the comprehensive integrated system for function profiling and information focusing on analysis of characteristics of biological resources in RIKEN BRC.
3. Construction of database for providing the information of biological resources collected in RIKEN BRC and network system linked to the other institutes for integration of related information.
4. Development of the new technique for anlysis of gene function in vivo.

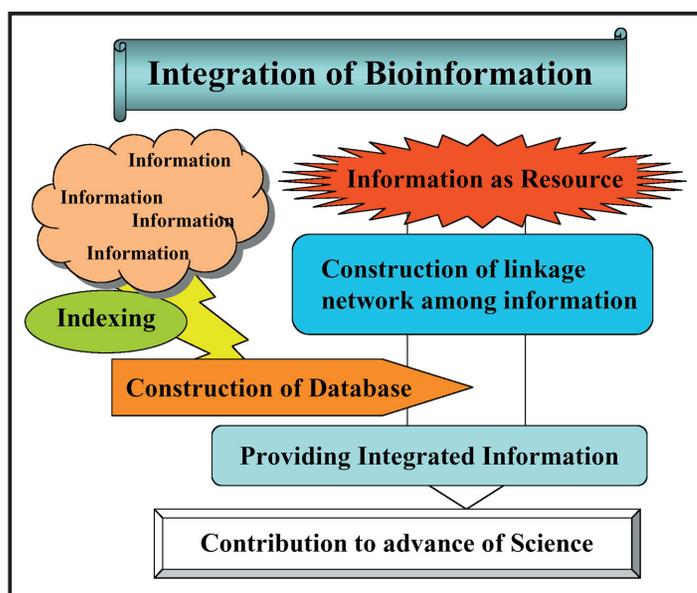


Figure 2.

Construction of database for providing the information of biological resources collected in RIKEN BRC and network system linked to the other institutes for integration of related information.

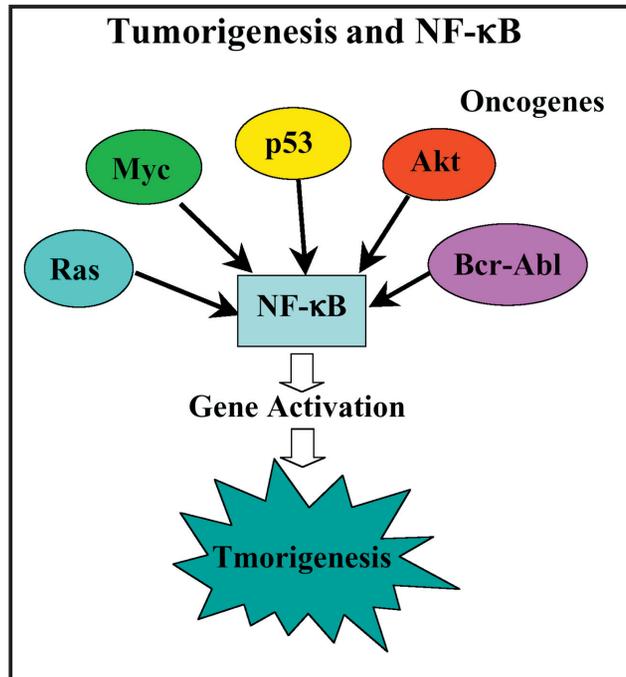


Figure 3.
Analysis of mechanism of tumorigenesis with the major transcription factors (NF-κB and AP-1).

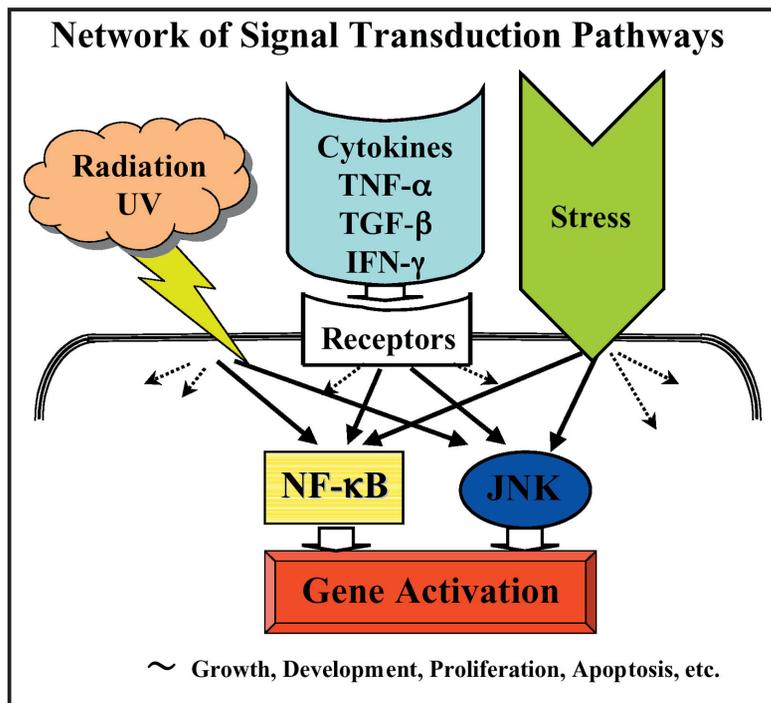


Figure 4.
Analysis of mechanism of signal transduction pathways for biological response against stimulation from outside focused on NF-κB and JNK.

- Publications**
- Okazaki T., Sakon S., Sasazuki T., Sakurai H., Doi T.-S., Yagita H., Okumura K., Nakano H. Phosphorylation of serine 276 is essential for p65 NF- κ B subunit-dependent cellular responses. *Biochem. Biophys. Res. Commun.* 2003; 300: 807-812
- Sakurai H., Suzuki S., Kawasaki N., Nakano H., Okazaki T., Chino A., Doi T.-S., Saiki I. Tumor Necrosis Factor- α -induced IKK Phosphorylation of NF- κ B p65 on Serine 536 Is Mediated through the TRAF2, TRAF5, and TAK1 Signaling Pathway *J. Biol. Chem.*, 2003; 278: 36916 - 36923.
- Sakon S., Xue X., Takekawa M., Sasazuki T, Okazaki T., Kojima Y., Piao J.-H., Yagita H., Okumura K., Doi T.-S., Nakano H. NF- κ B inhibits TNF-induced accumulation of ROS that mediate prolonged MAPK activation and necrotic cell death *EMBO J.* 2003 22: 3898-3909.
- Acuto O., Mise-Omata S., Mangino G., and Michel F. Molecular modifiers of T cell antigen receptor triggering threshold: the mechanism of CD28 costimulatory receptor. *Immunol. Rev.* 192, 21-31. (2003).
- Mise-Omata S., Montagne B., Deckert M., Wienands J., and Acuto O. Mammalian actin binding protein 1 is essential for endocytosis but not lamellipodia formation: Functional analysis by RNA interference. *Biochem. Biophys. Res. Comm.* 301, 704-710. (2003).
- Oral Presentations**
- Takahiro Doi, L. J. Old, M. W. Marino, V. Jongeneel, A. Viale: Analysis of TNF-induced NF- κ B /RelA-dependent gene expression. 61st Annual Meeting of the Japanese Cancer Association, Tokyo, 2003
- Setsuko Mise, Benjamin Montague, Marcel Deckert, Jurgen Wienands, Oreste Acuto: Mammalian actin binding protein 1 is essential for endocytosis but not lamellipodia formation: Functional analysis by RNA interference. 56th Annual Meeting of the Japanese Society for Cell Biology, Otsu, 2003