[Plant Signaling & Behavior 4:3, 165-167; March 2009]; ©2009 Landes Bioscience

Mini-Review

IAN/GIMAPs are conserved and novel regulators in vertebrates and angiosperm plants

Zhijuan Wang and Xia Li*

The State Key Laboratory of Plant Cell & Chromosome Engineering; Center of Agricultural Resources; Institute of Genetics and Developmental Biology; Chinese Academy of Sciences; Shijiazhuang, Hebei, China

Key words: IAN/GIMAP proteins, AIG1 domain, survival, stress response, immune response

The IAN (immune-associated nucleotide-binding protein) family belongs to a family of AIG1-like GTPases. These functionally uncharacterized GTP-binding proteins have unique structures and are differentially expressed in both vertebrate immune cells and plant cells during antibacterial responses. In mammals, the IANs, as a novel family of T cell receptor-responsive proteins, play critical roles in regulation of thymic development and survival of T lymphocytes through the interaction with Bcl-2 family proteins. The Arabidopsis AIG1 and AIG2, which are first identified IAN proteins, are involved in plant resistance to bacteria. Recent analysis of the expression patterns of Arabidopsis *IANs* suggests that these IAN proteins may play regulatory roles during plant development and response to both biotic and abiotic stress.

GTP-binding proteins are key components of biological complexes which control growth and development of eukaryotes under normal and stress conditions. IAN (immune-associated nucleotide-binding proteins (also known as GIMAP: GTPase of immunity-associated proteins) proteins belong to a novel GTPase family. Many IAN/GIMAP proteins have been found to present in both animal and plant cells. It is reported that the proteins function in the survival and development of T lymphocytes in mouse and human and in resistance responses in *Arabidopsis thaliana.*

What are IAN/GIMAP Proteins?

IAN/GIMAP proteins are a family of GTP-or/and ATP-binding proteins conserved in vertebrates and angiosperm plants, and they were named according to their most prominent function in development of immune system and regulation of immune responses. The first IAN/GIMAP protein was found in Arabidopsis and designated as AIG for avrRpt2-induced gene. The expression of *AIG1* is rapidly and transiently induced by infection with avirulent strains of Pseudomonas that caused a hypersensitive response leading to occurrence of necrotic lesions at the infection sites.[1] However, much of our understanding of the IAN/GIMAPs functions comes from studies of animals though they are initially described in plants. In animal cells, such as rat, mouse and human, the IAN/GIMAP mRNAs are expressed predominantly in immune tissues and play crucial roles in regulating T-cell development and in maintaining T-cell homeostasis for normal immune functions.[2-6]

Most of the *IAN/GIMAP* genes are clustered in both plant and vertebrate genome. For example, 12 of 13 *AtIAN* family members (above 90% of total *AtIANs*) are localized on chromosome 1 and 4 in a tandem array.[7] In mouse, eleven *IAN* genes were previously predicted to lie within a tight cluster on Chromosome 6, and a cluster of 10 human *IAN* genes was found to localize within about 300 kb in the chromosome 7.[6,8-10] Tandem gene duplication is considered as a key mechanism for the expansion of *IAN/GIMAP* gene family.[11]

All the IAN/GIMAP proteins have specific conserved amino acid domains: a AIG1 domain and a coiled-coil motif.[6,7] The AIG1 domain consists of five motifs (G1–G5) for GTP-binding and a conserved hydrophobic box between G3 and G4 unique to AIG1-like proteins.[6,12] Interestingly, the IAN/GIMAP proteins are localized at multi-sites including cytoplasm, ER, Golgi complex and mitochondria.[2,6,9,10,13] Distinct localization of the IAN/GIMAP protein members implies multiple modes of IAN mediated signaling pathways.

IAN/GIMAP Proteins as Key Regulators of Immune Response

The capacity of IAN proteins to stimulate immune response to infectious pathogens was first identified in Arabidopsis. Recent computational analysis showed that in addition to induction by Pseudomonas infection, *AtIAN8* (*AIG1*) is also highly inducible by *P. infestans* and syringolin, and is slightly promoted by salicylic acid. The expression levels of *AtIAN3* and *AtIAN11* are highly increased by the infection of nematode, while the transcripts of *AtIAN11*, *AtIAN12* and *AtIAN13* are repressed by *Myzus. Persicae*.[7] These results suggest that these *IAN/GIMAP* genes play important roles in biotic defense responses. The experimental analysis is needed to verify their functions in plant defense and the underlying molecular mechanisms.

The studies from human and mouse have provided clear and convincing evidence that the IAN/GIMAPs function as critical

*Correspondence to: Xia Li; The State Key Laboratory of Plant Cell & Chromosome Engineering; Center of Agricultural Resources; Institute of Genetics and Developmental Biology; Chinese Academy of Sciences; 286 Huaizhong Road; Shijiazhuang, Hebei 050021 China; Tel.: 86.0311.85871744; Fax: 86.0311.85815093; Email: xli@genetics.ac.cn

Submitted: 12/21/08; Accepted: 12/23/08

Previously published online as a *Plant Signaling & Behavior* E-publication: http://www.landesbioscience.com/journals/psb/article/7722

regulators in immune response. Most *IAN/GIMAPs* are predominantly and differentially expressed in immune system cells and tissues, such as the spleen and lymph nodes in both human and mouse.[8-10,14,15] For example, all eight members of the *IAN* family in mouse were expressed abundantly in the spleen and the lymph node. During T-cell development in the thymus, *IAN* genes such as *IAN1*, *IAN4*, *IAN5* are highly expressed in T lymphocytes and their expression is significantly elevated upon the maturation of DP to SP thymocytes.[9] Recently, more compelling evidence reveal the important roles of mammalian IAN/GIMAP family proteins in T-cell development, selection and survival, in controlling T-cell homeostasis, autoimmunity and leukemogenesis.[10]

For example, overexpression of *IAN1* in fetal thymus organ culture resulted in severe apoptosis of developing thymocytes, whereas *IAN1*-deficient mice showed a significant delay in cell death of peripheral T cells suggesting the role of *IAN1* in promoting T-cell death.[9,10,13] *IAN4* appears to support the positive selection of CD4 SP and CD8 SP T cells in the thymus because it is expressed greatly in DP thymocytes induced by TCR signals and the knockdown of *IAN4* in thymocytes resulted in a significant reduction of mature CD4 SP and CD8 SP thymocytes, and a compensatory accumulation of DP thymocytes.[9,10] The mature SP thymocytes and peripheral T cells of BioBreeding rat which carried a frameshift mutation in *IAN5* encoding a nonfunctional truncated protein showed accelerated apoptosis in cell culture.[16] The knockdown of *IAN5* expression in mouse immature thymocytes disturbs the subsequent generation of DP thymocytes in fetal thymus organ culture. These results indicate that *IAN5* is a key regulator in T-cell development and T-cell apoptosis.[9,10]

IAN/GIMAPs Regulate Cell Apoptosis through Mitochondria-Mediated Pathway in Mammals

The apoptosis of immune cells is very important to the immune-system development and the regulation of immune responses. In mammalian lymphocytes, cell apoptosis is regulated by three signaling pathways: mitochondria-mediated, death receptor-initiated and endoplasmic reticulum stress-mediated pathways. However, the molecular mechanism(s) of IAN/GIMAP mediated lymphocyte cell death and survival still remains unknown. Several lines of evidence strongly indicate that IAN1, IAN4 and IAN5 may function as fine regulators to control the process of cell death through the mitochondria-mediated pathway. IAN1 may promote apoptosis by activating the mitochondria-mediated pathway through its interaction with the pro-apoptotic protein Bax.[9] It may function downstream of caspase-3 in the signaling pathway and its phosphorylated state is important during the apoptosis process.[13] In contrast, the results of coimmunoprecipitation reveal that IAN4 and IAN5 regulate T cell apoptosis by interacting physically with the Bcl-2 family proteins, Bcl2 and Bcl-x_L.[9,10] Indeed, the knockdown of *IAN5* in T cells reduces the mitochondrial membrane potential of the cells and the cell survival,[17] while increasing expression of Bcl-x_L can restore the survival in *IAN5* knockdown T cells.[9]

Divergent Roles of IAN/GIMAP Proteins

Recently, divergent roles of IAN proteins have been noticed although they are well known for their functions in immune response. In Arabidopsis, 13 *AtIAN/GIMAP* genes show very distinct expression patterns and/or tissue specificity during plant development and response to various environmental stimuli by a computational approach.[7] For instance, *AtIAN13* is expressed mainly in pollen and *AtIAN4* is preferentially in radicle, whereas *AtIAN5* is expressed in pollen, cotyledon and lateral roots. The expression profiles of these genes suggest that they may temporally and spatially regulate organ development in plants. Furthermore, the gene expression analysis also reveals roles of AtIAN in plant response to abiotic stress. For example, the expression of *AtIAN5* and *AtIAN9* is increased by heat treatment. The expression of *AtIAN8* and *AtIAN9* is slightly increased by osmotic. Interestingly, *AtIAN8* (*AIG1*) and *AtIAN11* are responsive to both biotic and abiotic stress (e.g., cold), suggesting that these genes may be the promising candidates for common players that are involved in crosstalk between abiotic and biotic stress signaling pathways.

In mammals, differential gene expression patterns for IAN/GIMAP members have also been detected. Some genes are expressed at higher levels in non-immune tissues and cells such as *GIMP4* in human which is expressed in several organs of the reproductive system like placenta, prostate and testis except its expression in immune cells.[6] In addition, the physiological roles and molecular functions of some IAN/GIMAPs such as IAN12/GIMAP2 still remain unknown. We cannot exclude the possibilities that mammalian IAN/GIMAPs may also play diverse roles during development and in response to various stresses.

Conclusion and Perspectives

Much remains to be learnt about the IAN/GIMAPs biology. In Arabidopsis, more than a decade has passed since the first IAN protein was identified. However, it is still not known how the protein modulates the host immune response. Microarray results now suggest that AtIANs may play important roles in plant growth and development, as well as in responses to abiotic stresses. Therefore, attention should be paid to the physiological and molecular role of the IAN proteins and their intercellular signaling capacity in adaptation to their growth environment. An integrated reverse genetic approach is essential to elucidate the functions of AtIANs during their lifetime.

The importance of the IAN/GIMAP proteins in physiological and immunological processes has been confirmed in animals and human. The combined functional genomic, computational and proteomics approaches will further our understanding of the various immuno-regulatory mechanisms in which IAN/GIMAP proteins are involved. Those novel insights could help us to harness the power of these proteins for the control of inflammatory processes and the treatments of human diseases including cancers, diabetes and infections.

References

1. Reuber TL, Ausubel FM. Isolation of Arabidopsis genes that differentiate between resistance response mediated by the RPS2 and RPM1 disease resistance genes. Plant Cell 1996; 8:241-9.
2. Stamm O, Krucken J, Schmitt-Wrede HP, Benten WP, Wunderlich F. Human ortholog to mouse gene imap38 encoding an ER-localizable G-protein belongs to a gene family clustered on chromosome 7q32-36. Gene 2002; 282:159-67.
3. Hellquist A, Zucchelli M, Kivinen K, Saarialho-Kere U, Koskenmies S, Widen E, et al. The human *GIMAP5* gene has a common polyadenylation polymorphism increasing risk to systemic lupus erythematosus. J Med Genet 2007; 44:314-21.
4. Cambot M, Aresta S, Kahn-Perles B, Gunzburg JDE, Romeo PH. Human immune associated nucleotide 1: A member of a new guanosine triphosphatase family expressed in resting T and B cells. Blood 2002; 99:3293-301.

5. Zenz T, Roessner A, Thomas A, Frohling S, Dohner H, Calabretta B, et al. hIan5: the human ortholog to the rat Ian4/Iddm1/lyp is a new member of the Ian family that is over-expressed in B-cell lymphoid malignancies. Genes Immun 2004; 5:109-16.
6. Krüchen J, Schroetel RMU, Müller IU, Saïdan N, Marinovski P, Benten WPM, et al. Comparative analysis of the human gimap gene cluster encoding a novel GTPase family. Gene 2004; 341:291-304.
7. Liu C, Wang T, Zhang WS, Li X. Computational identification and analysis of immune-associated nucleotide gene family in *Arabidopsis thaliana*. J Plant Physiol 2008; 165:777-87.
8. MacMurray AJ, Moralejo DH, Kwitek AE, Rutledge EA, Yserloo BV, Gohlke P, et al. Lymphopenia in the BB rat model of type1 diabetes is due to a mutation in a novel immune-associated nucleotide (Ian)-related gene. Genome Res 2002; 12:1029-39.
9. Nitta T, Nasreen M, Seike T, Goji A, Ohigashi L, Miyazaki T, et al. IAN family critically regulates survival and development of T lymphocytes. Plos Biol 2006; 4:593-605.
10. Nitta T, Takahama Y. The lymphocyte guard-IANs regulation of lymphocyte survival by IAN/GIMAP family proteins. Trends Immunol 2006; 28:58-65.
11. Shiu SH, Bleecker AB. Receptor-like kinases from Arabidopsis form a monophyletic gene family related to animal receptor kinases. Proc Natl Acad Sci USA 2001; 98:10763-8.
12. Sprang SR. G protein mechanisms: insights from structural analysis. Annu Rev Biochem 1997; 66:639-78.
13. Schnell S, Démollière C, Berk P, Jacobs H. Gimap4 accelerates T-cell death. Immunobiology 2006; 108:591-9.
14. Poirier GM, Anderson G, Huvar A, Wagaman PC, Shuttleworth J, Jenkinson E, et al. Immune-associated nucleotide-1 (IAN-1) is a thymic selection marker and defines a novel gene family conserved in plants. J Immunol 1999; 163:4960-9.
15. Dahe'ron L, Zenz T, Siracusa LD, Brenner C, Calabretta B. Molecular cloning of Ian4: a BCR/ABL-induced gene that encodes an outer membrane mitochondrial protein with GTP-binding activity. Nucl Acids Res 2001; 29:1308-16.
16. Dalberg U, Markholst H, Hornum L. Both Gimap5 and the diabetogenic BBDP allele of Gimap5 induce apoptosis in T cells. Int Immunol 2007; 19:447-53.
17. Pandarpurkar M, Wilson-Fritch L, Corvera S, Markholst H, Hornum L, Greiner DL, et al. Ian4 is required for mitochondrial integrity and T cell survival. Proc Natl Acad Sci USA 2003; 100:10382-7.