Presentation of the funded projects in 2010 for the Blanc Inter SVSE 6 Programme

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« Blanc Inter SVSE 6 » Programme

2010 Edition

Project title	**ARBOAS** – Deciphering the role of Human OAS gene family in the pathogenesis of arbovirus infection

Abstract

Innate immunity plays a major role in the earliest stages of arbovirus infection. IFN-a/ß constitute the very first lines of antiviral innate immune response against arboviral infection. IFN-a/ß trigger the activation of IFN-stimulated genes such as members of IFN-induced 2', 5'-Oligoadenylate (OAS) family that play a critical role in the establishment of an antiviral state against RNA viruses such as flaviviruses (Dengue [DENV], West Nile [WNV] and Japanese encephalitis [JEV] viruses) and alphaviruses (Chikungunya [CHIKV] virus). DENV, WNV, JEV, and CHIKV are emerging zoonotic arboviruses of medical concern in France and Taiwan. OAS play important roles in the antiviral IFN pathway through the action of activated latent endoribonuclease, RNase L. The 1b isoform of mouse Oas1 has been identified as a flavivirus resistance gene in mice. The Human OAS gene family, is comprised of 4 genes, and following alternative splicing can encode 10 different isoforms. In this ANR-NSC joint call grant proposal, we propose a collaborative project between a French team consisting of 3 groups (molecular virology, biochemistry, and human genetics) at the Institut Pasteur, Paris (IPP) and a team of immunologists from the Institute of Biomedical Sciences (IBS), Taiwan. All teams have been working on the OAS gene family and have published several articles on this subject. The Flavivirus-Host Molecular Interactions (FHMI) group at IPP led by Dr DESPRES discovered a non-sense mutation in mouse Oas1b gene resulting in increased susceptibility to WNV. In vitro study showed that cells expressing Oas1b but not the C-terminally truncated Oas1b efficiently inhibited WNV replication. Genetic knock-in of the Oas1b resistance allele into a susceptible mouse strain confers mouse with resistance against Yellow Fever virus. Recently, FHMI in collaboration with the team at IPP led by Dr SAKUNTABHAI, observed that the large form of human OAS (OAS3) exerts RNase L-independent antiviral activity in

infected human cells against the wild-type virulent strain of CHIKV. Cells expressing a genetic variant , found at 2% allele frequency in Caucasians, lacks 20% of the C-terminus and were less resistant to CHIKV, raising the question of the role of OAS3 genetic polymorphisms in human susceptibility to alphavirus infection. The antiviral effect of human OAS family members against Dengue virus serotype 2 (DENV-2) has been studied by Dr LIN's laboratory, IBS Taiwan, who found that OAS1 p42, OAS1 p46, and OAS3 p100, but not the other gene family members, exhibited anti-DENV activity; these antiviral effects were largely lost in cells deprived of RNase L expression. Moreover, RNase L activity indicated that the human OAS1 p42, OAS1 p46, and OAS3 p100 triggered activation of RNase L during DENV replication. Thus, OAS1 p42/p46 and OAS3 p100 are likely to contribute to host defense against DENV and play a role in determining the outcome of DENV infection. Human OAS gene family was recently demonstrated in vivo and in vitro to contribute to susceptibility to WNV. Clinical evidence from WNV-seropositive patients showed that "A" allele at a SNP of OAS1, that generates OAS1 p48 and p52 but not p46, is a risk factor for the initial infection of WNV, supporting our data that OAS1 p42/p46 but not OAS1 p44/p48/p52 mediate a potent anti-DENV-2 activity and may contribute to host defense against DENV infection. We propose to study further the role of OAS in DENV, CHIKV and JEV infection. The mechanisms underlying the differential antiviral effects of the OAS gene family members and their isoforms require further investigation. In addition, the role of these enzymes in natural human infections of DENV and CHIKV is not known. We, therefore, propose a program that combines expertise from the IBS, Taiwan and IPP, France with the aim of understanding the mechanisms underlying the differential anti-viral activity of the human OAS gene family and their role in natural infections.

Partners

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Project title	**Legumics** – Expanding tools for legumes and demonstrating their power in root and symbiotic nodule development studies.

Abstract

Legume plants are used in agriculture as a protein source for human and animal nutrition and may represent the unique protein source for human nutrition in some countries. The high protein content of legume plants is achieved via the establishment of a root symbiosis with nitrogen fixing rhizobia. Establishment of this symbiotic interaction occurs when the soil nitrogen source is limiting and results in the formation of a dedicated root organ called the root nodule inside which rhizobia fix nitrogen. The development of the legume root system is not only determined by their ability to interact with symbiotic microorganisms but also by the distribution and number of lateral roots. In order to adapt their root architecture to cope with nutrient starvation and abiotic stresses, legumes have developed specific strategies, which are likely different from those of the reference plant A. thaliana which is unable to develop symbiotic interactions. Interestingly, several lines of evidence indicate that nodules and lateral roots formations are integrated into regulatory mechanisms affecting the whole root system in response to environmental changes. Thus, the use of legumes in modern agriculture will require understanding various aspects of legume development such as the symbiotic interaction with rhizobia, that can be used to reduce nitrogen input to the culture, but also root architecture that will condition access to nutrients. Model plant organisms proved to be useful to answer biological questions that are more difficult to study in cultivated species. Medicago truncatula is recognized as an excellent legume model in view of its small, diploid genome, self-fertility, and short life cycle, as well as availability of various genomic and genetic tools. We now know that genetic and genomic tools developed for this plant can be readily applied to the important crop species such as alfalfa, pea and Faba bean as the result of their close genome relationship. This gives the opportunity to directly apply results obtained with this plant to legume crops. The use of tagged mutant collections is essential to reveal gene functions and to uncover the genetic interactions such as those that underlie plant responses to the environment and development. For example, genetic studies based on tagged mutant collections have been extensively used in Arabidopsis and

sequencing of the T-DNA insertion sites in mutant collections and availability of this information as a web resource represents a very important tool for the scientific community. An insertion mutant collection based on the use of retroelements Tnt1 and MERE1 was developed in M. truncatula during the EU GLIP project (www.eugrainlegumes.org) in parallel to the one existing at the Noble foundation (http://bioinfo4.noble.org/mutant/), but in the case of the GLIP collection, only the construction of the collection was financed despite the value of such collections for the community. The purpose of this French/Hungarian ANR academic project is to further develop and use the genomic resources established for the model legume M. truncatula. For this, we propose to use the insertion mutant collections developed in the frame of the FP6 Grain Legume Project in order to i) develop a high throughput sequencing method for sequencing the insertion sites in a large number of the existing insertion mutant lines, ii) apply this technology to sequence the majority of the tagged loci in a large part of this mutant collection iii) perform genetic screens in order to identify mutants affected in nodule functioning and root development, iv) use the sequence information to identify the tagged genes in these mutants and v) characterize at the molecular, physiological and cellular levels some of the identified mutants.

Partners	CNRS Institut des Sciences du Végétal CNRS Institut des Sciences du Végétal Agricultural Biotechnology Center (Hongrie) Biological Research Center Institute of Genetics Medicago Genetics Group (Hongrie) Bay Zoltán Foundation for Applied Research Institute of Plant Genomics, Human Biotechnology and Bioenergy (BAYGEN) (Hongrie)
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