A. MOLECULAR MEDICINE AND HUMAN GENETICS
Head: GEORGE N. GOULIELMOS, PhD

BACKGROUND

The bidirectional interaction between basic and clinical sciences in Medicine, have provided the impetus to the rapid development of Molecular Medicine. The nature and extent of the genetic contribution to human variation and disease is the area of interest of a related field, that of Human Genetics. Most of the genes involved in the major monogenic disorders, which follow Mendelian patterns of inheritance, have now been isolated and characterized; however, their overall population incidence in the population is relatively low. On the other hand, complex (or multifactorial) diseases such as cancer, diabetes, rheumatoid arthritis, coronary artery disease etc, result from the interaction of multiple genetic and environmental factors. This group of diseases represents the most common and the least understood human diseases. Identification of genetic factors predisposing individuals to diseases is a powerful tool since offers the opportunity for prevention or treatment of several human diseases.

RESEARCH

The long-term goal of G. Goulielmos' group is to approach the Familial Mediterranean Fever (FMF) disease from several points of view, including epidemiologic, populational, biochemical and structural biology aspects, with the ultimate task being to depthen further the existing pathogenic mechanisms and gain insight into new molecular pathways leading to the development of FMF. To this end, we use human samples from patients followed by the Internal Medicine and Rheumatology clinics of the University Hospital. Moreover, the study of the genetics of complex diseases represents another major area of the laboratory research. Altogether, the Goulielmos' group engages in three specific areas of research:

1. Genetics / molecular pathways in recurrent fever syndromes such as Familial Mediterranean Fever (FMF)

FMF, the prototype of a group of diseases referred to as hereditary recurrent fevers, is characterized by episodes of seemingly unprovoked inflammation involving the abdomen, the pleura, the pericardium and the joints. It is inherited in an autosomic recessive manner and the gene responsible for FMF is MEFV, which encodes for the pyrin protein. Whilst Greek population was considered to be at “intermediate risk” for FMF, preliminary results had shown that the incidence of FMF appeared to be higher in the island of Crete.

Our research is focused on the analysis of the spectrum of MEFV gene mutations both in FMF patients as well as in healthy controls from Crete. The correlation of specific genotypes with clinical manifestations is also under examination. A 3-D model of the PRYSPRY domain of pyrin (harbouring the majority of the severe or mild mutations) has been constructed in collaboration with Prof. E. Eliopoulos (Agric. Univ. of Athens) and the MEFV mutations have been localized on it according to their clinical severity. In collaborative studies with the groups of Drs D. Kastner and I. Aksentijevich (NIH, Bethesda, USA) and Prof. D. Gumucio (Univ. of Michigan, USA), we attempt to detect alternative pathogenic pathways leading to FMF (Figure). In particular, the finding of a putative interaction between SIVA protein and the PRYSPRY domain has prompted us to further explore the potential contribution of the aforementioned interaction to the pathogenesis of FMF by studying the ability of mutant forms of pyrin to prevent the apoptotic cascade initiated by the CD27/SIVA interaction.

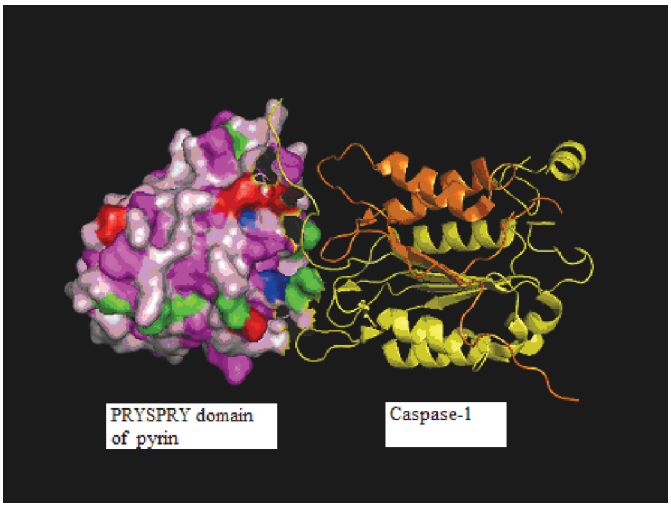

Figure. *The alternative explanation presented recently suggests a direct interaction of PRYSPRY domain of pyrin with caspase- 1 in order to modulate the IL-1b production in FMF. This second mechanism for the pathogenesis of FMF has some areas that need further refinement. According to a new 3-D model constructed by our group, the "flexible loops" of caspase-1 may have no access to some positions of pyrin causing mild disease, which are located in the back surface of the binding cavity of PRYSPRY.*).

2. Genetics of complex human diseases

Several genetic polymorphisms have been associated so far with different vascular, infectious and autoimmune diseases in several ethnic populations. The objective of this project is to investigate whether genetic polymorphisms of several candidate genes (i.e. eNOS, PD.1, PTPN22, TLR-2, TLR-4, VDR, MBL) play any role as predisposing or severity factors in the pathogenetic processes of diseases such as Systemic Lupus Erythematosus, Rheumatoid Arthritis, Type 1 and 2 Diabetes Mellitus as well as a variety of infectious diseases including Acute Otitis Media and Chronic Hepatitis C. This is the first time that these genetic polymorphisms are explored in subjects from island of Crete, who share the same genetic and cultural background as well as a common environment and this type of studies may be considered as a fist step towards a broader molecular diagnosis approach of Cretan population.

3. Genetic / molecular pathways of other metabolic diseases

In collaboration with other groups we explore issues on molecular biology of hyperlipidemia and other disorders of the lipoproteins pathways.

REPRESENTATIVE PUBLICATIONS

1. Goulielmos, G.N., Fragouli, E., Aksentijevich, I., Sidiropoulos, P., Boumpas, D.T., and Eliopoulos, E (2006). Mutational analysis of the PRYSPRY domain of pyrin and implications for Familial Mediterranean Fever (FMF). Biochem. Biophys. Res. Commun. 345:1326-1332.

2. Vazgiourakis, V., Sidiropoulos, P., Bertsias, G., Raptopoulou, A., Koutsounaki, E., Fragouli, E., Kritikos, H., Boumpas, D.T. and Goulielmos, G.N. (2007). Association of the nitric oxide synthase gene (eNOS) polymorphism with increased risk for rheumatoid arthritis - but not for systemic lupus erythematosus - in population of Crete, a southern-eastern European Greek island. Lupus (in press).

3. Fragouli, E., Eliopoulos. E., Petraki, E., Sidiropoulos, P., Aksentijevich, I., Galanakis, E., Kritikos, H., Repa, A., Fragiadakis, G., Boumpas, D.T. and Goulielmos, G.N. (2007). Familial Mediterranean Fever (FMF): a genetic and structural biological approach of the disease in Cretan population, a population of “intermediate risk”. Clinical Genetics (accepted with revisions).

4. Fragouli, E., Eliopoulos, E., Sidiropoulos, P., Aksentijevich, I., Boumpas, D.T. and Goulielmos, G.N. (2007). Three dimensional (3-D) model of the PRYSPRY domain of pyrin: implications for disease severity in Familial Mediterranean Fever (FMF). Abstracts of the 27th

European Workshop for Rheumatology Research, Firenze, Italy, February 22-24. Annals of the Rheumatic Diseases 66 (s1):A32.

5. Fragouli, E., Eliopoulos, E., Petraki, E, Galanakis, E., Sidiropoulos, P., Aksentijevich, I., Kritikos, H., Fragiadakis, G., Boumpas, D.T. and Goulielmos, G.N. (2007). Familial Mediterranean Fever (FMF): a genetic approach in the Cretan population and structural implications of the pyrin PRYSPRY domain interactions. EULAR Meeting, Barcelona, Spain, June 12-17, Annals of the Rheumatic Diseases 66 (s11):128

6. Eliopoulos, E., Kyrmizi, I., Boumpas, D.T. and Goulielmos, G.N. (2007). Mapping the sequence of the human Tpl2 to a structural model: implications to signaling defects. Proceedings of the 71st Annual Meeting of the American College of Rheumatology (ACR/ARHP Scientific Meeting 2007), Boston, USA, November 6-11, Arthritis and Rheumatism (supplement), in press.

GROUP MEMBERS

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FUNDING

FP5 European Program for quality of life and management of living resources
FP6 European AUTOCURE Program
The Hellenic Society of Rheumatology

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