INTRODUCTION

In 2001, an NIH working group standardized the definition of a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" and defined types of biomarkers

Our ability to study and treat diseases including diabetes, heart diseases, obesity and metabolic syndrome is hampered by a lack of unique, reliable, quantifiable, easily measured biomarkers that correlate well with disease progression. The clinical presentation of these chronic diseases is more often at a stage at which reversal or optimal control is very difficult. Compounding the problems in disease management is the non-availability of methods for monitoring disease progression or the efficacy of potential therapeutic interventions short of frank, clinically observable signs or symptoms. Similarly, clinical trials are especially difficult to design for chronic diseases. These trials for new therapies are often impractical or very expensive; since large numbers of patients must be followed for the long periods of time needed to achieve hard clinical endpoints such as non fatal MI or MI caused deaths. Therefore, robust biomarkers for cardiovascular diseases and diabetes need to be developed. These must be quantifiable and correlate well with clinical and biochemical measures of disease progression, and should be relatively inexpensive and noninvasive so that they can be measured serially over time. Efforts are also required to identify biomarkers which can reduce the need to achieve hard clinical endpoints in clinical trials, and would therefore help to lower the associated costs by reducing the number of patients needed and the time during which they are monitored.

Fueling interest in the development of biomarkers is the emergence of new technologies like genomics, proteomics and metabolomics that come with the promise of enabling researchers to capture molecular fingerprints of heart diseases as well as diabetes. The fine tuning of understanding of disease processes may lead to discovery of new markers helpful for screening of people at risk of heart diseases/ diabetics who progress towards coronary artery disease. Given the potential of these biomarkers in detection and treatment, these markers could have a role in altering the burden of these diseases.

However, despite the promises which biomarker research makes, only few biomarker based tests for heart diseases and diabetes have entered the market. Furthermore translation of basic science research on biomarkers into clinically useful tests is lagging. The challenges are many and encompass technical, regulatory, financial and social challenges linked to discovery, development, validation and incorporation of these tests in clinical practice. To explore the biomarkers which can be translated into clinical tests for screening, diagnosis, treatment and prognosis of the diseases and to understand the challenges involved in development, validation and incorporation of these markers a collaborative ICMR INSERM workshop on “Development of Biomarkers for Cardiovascular Diseases and Diabetes” was held in Gurgaon, India from 22nd to 24th Jan 2007.

AIM

The aim of this workshop was to provide a forum for identifying current research opportunities and prioritizing research areas which could be undertaken as ICMR-INSERM collaborative projects.

The workshop had following sessions:

Session I: Linking Obesity to Development of Heart Diseases and Diabetes

Session II: Inflammatory Responses as a Marker for Development of CVD and Diabetes

Session III: Linking Genes to Diabetes and Cardiovascular Diseases

Session IV: Predicting and Monitoring Diabetes

Session V: Diabetes and Cardiovascular Diseases

Session VI: Modus Operandi for Development of Research Proposals for Indo French Collaborations

In addition, the participants explored the recent advances in biomarker research in two group discussion sessions and one working group:

Roundtable: Reality Check 2007
Roundtable: Critical Paths to Biomarker Development
Working Group: Identification of Disease Risk: Genetic/ Genomic Approaches

Session I: Linking Obesity to Development of Heart Diseases and Diabetes
Chairpersons: F. CAMBIEN (France), NK GANGULY, BELA SHAH (India)

Obesity, Central Adiposity: Epidemiological Studies on Their Roles in Diabetes and Cardiovascular Diseases
Beverley Balkau, INSERM U780-IFR69

Obesity and central adiposity are already a pre-occupying problem of public health concern, on all continents and across socio-economic levels. The prevalence has increased markedly over the last decades and obesity is occurring at younger ages.

It has long been recognized that higher BMIs are associated with a risk of incident type 2 diabetes, and a central fat distribution appears to be a stronger risk factor than overall obesity. With increasing obesity, diabetes prevalence is also on the increase, and in turn, diabetes is associated with at least a doubling of risk for cardiovascular diseases.

As for cardiovascular disease, it is only more recently that the obesity has again been brought into focus. In particular the INTERHEART study, an international case-control study of myocardial infarction has shown that obesity and in particular central obesity, is a potent risk factor.

While cardiovascular disease has recently been on the decrease with better treatment for hypertension and lipids and the control of smoking, the increase in obesity and diabetes are likely to reverse this trend.

Clinical trails, such as the Finnish Diabetes Prevention Study, the American Diabetes Prevention Program and the Indian Diabetes Prevention Study show that lifestyle intervention can slow the progression to diabetes, of individuals with hyperglycemia.

Human Obesity; From Genetics to Transcriptomic Approaches
Karine Clément, INSERM U755 Nutriomique, Paris, F-75004 France; Pierre and Marie Curie -Paris 6 University, Faculty of Medicine, Les Cordeliers, 75004 Paris, France; AP-HP, Hôtel-Dieu Hospital, Nutrition Department, 75004 Paris, France.

Advances in genetics have made remarkable progress towards our understanding of body weight regulation. Much of our current knowledge has come from the cloning and characterization of the genes responsible for obesity syndromes and the identification of mutations causing rare forms of human obesity. However, the genetic determinants that underlie common forms of human obesity are largely polygenic, where one gene has a slight effect on weight. Elucidating the genetic factors of common obesity remains a challenge for researchers. Despite the inherent difficulties, progress has been made through the use of “omic” strategies to study the influence of nutrition and gene-environment interactions in human obesity. The goal of this conference was to provide some examples to explain how the “omic” approaches, and particularly transcriptomics, contribute to advancing our knowledge of human obesity and identifying biomarkers linking obesity to its complications. Finally, the future will undoubtedly witness the combining of various approaches, including transcriptomics, proteomics and information obtained from genetic analyses to improve our understanding of this complex disease.

Visceral Obesity and Haemostatic Abnormalities.

I Juhan-Vague, M.C. Alessi. Lab Hématologie, Faculté de Médecine ; Inserm UMR 626. Marseille France

Metabolic syndrome (MS) is a world wide epidemic, setting the stage for type 2 diabetes and vascular complications. It is a clustering of risk factors including visceral obesity, insulin resistance, dyslipidemia, hypertension and chronic low grade inflammation. A prothrombotic state due to disturbances in haemostasis and fibrinolysis, is now well documented in obese subjects with visceral obesity and could contribute to accelerated atherosclerosis. These alterations are the consequences of complex interrelations between insulin resistance, inflammation and the oxidative stress which occur at the level of ectopic fat depots, cardiovascular tissues and circulating cells.

An up regulation of proinflammatory cytokines leads to disturbances in the function of the vascular endothelium reflected by impaired endothelium-dependent vascular relaxation, increased secretion of endothelium derived products such as von Willebrand factor. Endothelial cells take a proadhesive phenotype (increased expression of VCAM, ICAM, E selectin…). There is an increased release of microparticules, and decreased number of endothelial cell progenitors which lead to a decreased regenerative potential.

In vitro studies have shown a number of anomalies in platelet functions in MS subjects. Hypertriglyceridemia and adiponectin deficiency facilitate platelet aggregation. These anomalies account for hypersensitivity of platelets to aggregants and hyposensitivity to antiaggregants and are thought to contribute to enhanced atherosclerosis via increased platelet activity at sites of vessel injury and could be involved in the platelet resistance to antiaggregating agents such as aspirin described in type 2 diabetic patients.

MS syndrome also has features of a hypercoagulable state, consisting of increased levels of clotting factors produced by the liver (factor VII and fibrinogen). Recently the highly vascularized adipose tissue has been proposed as a major source of tissue factor involved in the initiating step of coagulation. Its expression level and the resultant thrombin formation are influenced by insulin and glucose illustrating a possible link between glucose homeostasis and thrombosis.

The delay to thrombolysis observed in obese subjects is the most documented anomaly described in the MS. It has been attributed to increased PAI-1 levels. PAI-1 is an acute phase protein and the main antagonist of plasminogen activators. Beyond its function as an antifibrinolytic molecule, PAI-1 participates in processes involving angiogenesis and wound healing. Ectopic fat depots (peritoneal fat, liver steatosis, pericardiac fat…) may represent privileged sites of PAI-1 synthesis during the MS. Interestingly there is also increasing evidence that PAI-1–dependent mechanisms may contribute to the pathogenesis of obesity and type 2 diabetes mellitus.

In conclusion the last two decades of vascular biology research have yielded much information on the biochemical and cell biology factors involved in the vascular risk associated with visceral obesity and it is hoped that this will lead to the discovery of agents that directly target these mechanisms. It is plausible that PAI-1 inhibitors might serve both in the control of atherothrombosis and insulin resistance.

Cardio-Metabolic Inflammatory Risk in Asian Indians: Focus on Young Individuals.

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Several studies suggest that Asian Indians are predisposed to develop type 2 diabetes as well as coronary artery disease. This heightened metabolic risk starts early in childhood and escalates with imbalanced diet and sedentary lifestyle. Some of the important and distinguish characteristics of Asian Indians which increase chances of hyperglycemia and atherosclerosis are; excess adiposity, abdominal obesity, insulin resistance and metabolic syndrome, hepatic steatosis, sub-clinical inflammation and endothelial dysfunction. Some of these manifestations appear during early childhood. It is important that the metabolic risk factors should be targeted early in life to prevent development of diabetes and coronary artery disease in adults. For adult Asian Indians, a comprehensive and intensive risk reduction is necessary to decrease cardiovascular risk.

Diseases of Adipose Tissue: Genetic and Pathophysiology of Human Lipodystrophies

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Lipodystrophy is a disorder of adipose tissue characterized by a selective loss of body fat associated, or not, with fat accumulation in other depots. Patients with lipodystrophy develop insulin resistance frequently associated with dyslipidemia and altered glucose tolerance or diabetes, leading to fatty liver and atherosclerosis. There are numerous forms of lipodystrophies either genetic or acquired. However, whatever the origin, the common set of metabolic disturbances indicates the deleterious role of fat loss through altered adipokine production and/or ectopic fat deposition leading to lipodystrophy. Genetic forms are rare. Congenital generalized lipodystrophy, characterized by a complete early lipoatrophy and severe insulin resistance, results, in most cases, from mutations either in the seipin gene of unknown function or in *AGPAT2* encoding an enzyme involved in triglyceride synthesis. The Familial Partial Lipodystrophy of Dunnigan (FPLD2) is due to heterozygous mutations in *LMNA* encoding lamin A/C and belongs to the complex group of laminopathies, which also includes syndromes of premature aging. FPLD3 is linked to heterozygous mutations in the PPAR-γ gene. The acquired forms include forms related to antiretroviral treatment of HIV infection and to hypercorticism. In some of these diseases, adipose tissue is the site of an inflammatory process, with the presence of macrophages and the release of proinflammatory cytokines such as TNF□, IL-6 and IL-1□, involved in the patients' altered metabolic status and insulin resistance. Adiponectin and leptin are generally decreased and restoration of leptin levels improves insulin resistance and metabolic alterations. Pathophysiology of human lipodystrophies involves in addition to insulin resistance, mitochondrial dysfunction, increased oxidative stress, and altered cytokine production which could also result in a phenotype of premature aging.

Session II: Inflammatory Responses as a Marker for Development of CVD and Diabetes

Chairpersons: JACQUELINE CAPEAU (France), NK MEHRA (India)

Immunogenetic Biomarkers for Type 1 Diabetes in the North Indian Population

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MHC haplotypes carrying DRB1*03 have been implicated in several autoimmune diseases including type 1 diabetes, myasthenia gravis, celiac disease, SLE and others. However, the extent of association varies ethnically and could be explained partially on the basis of variability in HLA-DR3 haplotypes. A set of unique DR3 positive haplotypes have been identified in the Indian population in association with autoimmunity. The present study has evaluated molecular diversity of HLA-DR3 allelic family and divergence of DR3 associated haplotypes in 893 healthy North Indian people. The study has revealed that (i) the classical Caucasian AH8.1 (HLA-A1 B8 DR3) is rare in the Indian population and has been replaced by a variant AH8.1v that differs from the Caucasian AH8.1 at several gene loci (ii) AH8.2 (HLA-A26 B8 DR3) is the most common DR3 haplotype in the Indian population that resembles the Indian AH8.1v rather than Caucasian AH8.1 (iii) there are additional HLA-DR3 haplotypes HLA-A24B8DR3 (AH8.3), A3B8DR3 (AH8.4) and A31B8DR3 (AH8.5) that occur in the Indian population (iv) these Indian DR3 haplotypes (AH8.1v, AH8.2 and others) differ from the Caucasian AH8.1 at multiple loci e.g. HLA-Cw*0702, HLA-DRB3*0202 and several other markers (v) these DR3 positive haplotypes occur at relatively higher frequency in Indian patients with autoimmune diseases including T1D, Celiac disease etc. It has been hypothesized that AH8.1 and AH8.1v might have coevolved from a common ancestor but preferential divergence of AH8.2 over AH8.1 leading to survival advantage might have been driven by vigorous pathogenic challenges encountered by the Indian population. In addition to above, B18-DR3 and B58-DR3 might also play an important role in autoimmune diseases and is being investigated further.

Novel Biomarkers of Cardiovascular Risk.

Alain Tedgui, Inserm U689, Lariboisiere hospital, Paris

Current assessment of risk of cardiovascular events in apparently healthy individuals relies mostly on scoring using schemes such as the Framingham risk score or the Euroscore. These schemes rely on traditional risk factors for atherosclerosis like age, gender, smoking, hypertension, cholesterol, and diabetes. There is currently an immense interest in adding biochemical markers to these algorithms although the best marker(s) have yet to be identified. One of the extensively studied marker is *hs-CRP* and is the most advanced clinical marker. The American College of Cardiology (ACC) and the American Heart Association (AHA) have however restricted its usefulness to patients at mild to moderate risk while the European Society of Cardiology (ESC) has not included it in its prevention recommendations. The unspecific nature of *hs-CRP* highlights a great need and potential for new tools providing more specific risk information through the use of novel markers, or combinations of markers. There is also an unmet need for markers to address the risk of recurrent events in acute coronary syndromes and/or stroke patients. Phospholipase A2 (PLA2) enzymes hydrolyze phospholipids at the *sn*-2 position to generate lysophospholipids and fatty acids, leading to the activation of various immuno-inflammatory processes related to the pathogenesis and complications of atherosclerosis. We hypothesized that direct and accurate measurement of circulating secretory PLA2 (sPLA2) enzyme activity, which encompasses several types of

sPLA2, could be a better indicator of the potential pro-atherogenic properties of these enzymes than the measurement of a particular sPLA2 mass level. We first showed that plasma sPLA2 activity was an independent predictor of death and new or recurrent myocardial infarction in patients with acute coronary syndromes, and provided a better prognostic value than the measurement of sPLA2 type IIA mass or hs-CRP levels. We also provided evidence from a very large community-based prospective cohort (EPIC-NORFOLK) for a pro-atherogenic role of sPLA2 activity in humans. During the mean observational period of 6 years, a significant and independent increase in the incidence of CAD was observed with increasing baseline levels of sPLA2 activity. The association was independent of traditional risk factors and hs-CRP. Furthermore, sPLA2 activity had a significant predictive value on top of the Framingham risk score, and the combined measurement of sPLA2 activity and hs-CRP allowed a better assessment of the risk of incident CAD than measurement of either biomarker alone. Interest of another novel biomarker, circulating microparticles, will also be discussed. We recently reported that circulating leukocyte-derived microparticles are independently involved in the pathogenesis of sub-clinical atherosclerosis burden, and their quantification may provide additional option for risk stratification and offer new therapeutic target of risk reduction for primary prevention of cardiovascular disease.

A Role for the NKG2D Pathway in Type 1 Diabetes?

Sophie Caillat-Zucman, INSERM U561

Maintaining effective immune surveillance towards infected, transformed, and otherwise stressed cells without provoking autoimmune reactions is the goal of NK and T cells. This requires the precise titration of their effector function, which involves the integration of negative or positive signals transduced by inhibitory or activating receptors. The activity of NK cells is controlled by inhibitory and activating receptors whose ligands are present on potential target cells. Normally, NK cells are held in check by negative regulation by a large number of inhibitory receptors that recognize normal cells. To overcome this inhibition, transformed or infected cells can either diminish the ligands of the inhibitory receptors (mostly MHC class I molecules) or increase the expression of the ligands for the activating receptors. It is the balance in expression of these different ligands that determines NK cell activation versus inhibition, and therefore whether a cell becomes a target for NK cell-mediated killing. This also means that, depending on which cells become targets, NK cells can induce or regulate autoimmunity. In T cells, the expression of stimulatory receptors provides a mechanism through which TCR activation can be augmented, and through which the threshold for T-cell activation by self-antigens can be lowered. Therefore, apart from their crucial role in immune response to pathogens and tumors, NK receptors and their ligands must be considered as potential players in the induction or control of autoimmune disorders.

MICA/B are stress-induced molecules acting as a danger signal to alert NK cells and CD8 T lymphocytes through engagement of the NKG2D activating receptor. At variance with classical MHC class I molecules, MIC are specialized for reporting stress without the requirement for peptide binding, and can direct NK and T cells to kill transformed or infected cells. Since NKG2D is expressed on all human NK and CD8 T cells, acquisition of its ligands at the cell surface of potential target cells may be a triggering event leading to the breakdown of tolerance. MIC molecules, if non-specifically induced by an inflammatory process, or inappropriately expressed in predisposed individuals, might trigger or exacerbate an autoimmune disorder. Indeed, data from the literature strongly support the idea that NKG2D activation pathway participates in the development of immune-mediated diseases

The involvement of NKG2D and its ligands in autoimmune diseases was first revealed in rheumatoid arthritis (RA). The severity of RA is known to correlate with the presence of large numbers of CD4+CD28- T cells in peripheral blood and synovial tissue. These CD4 T cells

were found to express NKG2D, which is normally absent on CD4 T cells. NKG2D was induced by TNF and IL-15, which are abundant in inflamed synovia and sera of RA patients. In addition, RA synoviocytes aberrantly expressed the MIC ligands, which stimulated proliferation and IFN release by autologous CD4+ CD28- T cells. These data therefore indicated for the first time that a profound dysregulation of NKG2D and abnormal expression of MIC in local tissue environment could cause autoreactive T cell stimulation, thus promoting the self-perpetuating pathogenic process in RA.

Celiac disease (CD) is an immune-mediated disease of the small intestine, triggered by dietary gluten proteins, in particular gliadin. The lesion is characterized by villous atrophy, cryptic hyperplasia, and infiltration of the small intestine by activated CD4 T cells in the lamina propria and CD8 T cells in the epithelium. There is strong evidence for a central role of the CD4 T cell mediated recognition of gliadin in the disease process. In addition, the massive infiltration of intestinal epithelium by CD8 T lymphocytes represents one of the diagnostic hallmarks of the disease. Because MIC molecules have been localized to gut epithelium, an explanation to the participation of IELs in the pathogenesis of CD would be their unchecked expression within the intestine. We recently showed that MIC proteins were strongly expressed at the cell surface of epithelial cells in CD patients with active disease. They disappeared from the cell surface during gluten-free diet, but were again upregulated both in the epithelium and lamina propria of treated patients following gliadin challenge. Moreover, we observed that in vitro culture of biopsies from treated CD patients with gliadin-derived peptides led to over expression of MIC, and this effect was inhibited by antibodies neutralizing IL-15, a pro-inflammatory cytokine highly expressed in the intestinal epithelium of untreated CD patients. MIC-expressing enterocytes thus became the targets of NKG2D+ cytotoxic IELs that mediated villous atrophy. These data pinpoint the crucial role of innate immune response in the damage of intestinal mucosa, which is primarily due to the cytolysis of epithelial layer mediated by IELs activated through NKG2D. These data also provide a scheme linking the early activation of the innate cells and the CD4-mediated immune responses.

Insulin-dependent diabetes mellitus, or type 1 diabetes (TID), is an autoimmune disease in which insulin-producing cells in pancreatic islets are destroyed by autoreactive T cells. The nonobese diabetic (NOD) mouse is widely studied as a model of human TID. The development of autoimmune diabetes in NOD mice requires both CD4 and CD8 T cells. Inflammation of pancreatic islets (insulitis) is observed in 3-week-old NOD mice, but for unknown reasons, insulitis does not progress to diabetes until after 10 weeks of age, even if T cells have infiltrated into the pancreas. It was recently shown that NKG2D is involved in the development of autoimmune diabetes in the mouse. Islet cells in the prediabetic NOD mice (but not young healthy mice) expressed the Rae-1 ligands of NKG2D, and autoreactive CD8 T cells infiltrating the pancreas expressed NKG2D. At variance with human, mouse NKG2D is not present on naive CD8 T cells but is induced only after TCR-mediated activation. Interestingly, treatment with a nondepleting anti-NKG2D antibody during the prediabetic stage completely prevented the development of diabetes by impairing the expansion and function of autoreactive CD8 T cells, thus demonstrating that NKG2D is crucial for the progression of T1D. Why RAE-1 genes are expressed preferentially in the pancreas of NOD mice is unresolved. One possibility is that pancreatic cells inadvertently express RAE-1 genes as a consequence of the NOD genetic background. Although polymorphisms of human MICA have been associated with a variety of autoimmune disorders, including T1D, the functional relevance of such polymorphisms is so far unclear, and MICA associations frequently reflect a linkage disequilibrium with HLA-B alleles.

For technical and ethical reasons, it is impossible to have access to the target organ in prediabetic or diabetic patients, but induction of NKG2D ligands can be studied on islet cells freshly isolated from pancreas obtained from cadaveric donors, and cultured *in vitro* in presence of various factors such as cytokines or high concentrations of glucose. If NKG2D ligands are induced within the pancreas due to inflammation, or inappropriately expressed in

genetically predisposed individuals, this might co stimulate autoreactive CD8T cells, thereby inducing or exacerbating the disease. Another hypothesis is that CD4 T cells from susceptible individuals aberrantly express NKG2D, which is normally absent on CD4 T cells. NKG2D could be induced by proinflammatory cytokines, such as TNFα (or IL-15), and NKG2D+ CD4 T cells could participate in the insulitis through enhanced proliferation and/or production of IFNγ

In conclusion, it appears that, while NKG2D may provide beneficial in surveillance against cancer and infections, this system may have a detrimental role in some autoimmune disorders, either by dysregulated expression of the NKG2D receptor or by acquisition of its ligands on normal cells. Data reporting on the role of NKG2D activation in immune-mediated diseases suggest that different players in this activation pathway (NKG2D, MIC, IL-15) might be good targets for therapeutic intervention.

Session III: Linking Genes to Diabetes and Cardiovascular Diseases

Chairpersons: I JUHAN VAGUE (France), S MAJUMDAR (India)

Genomic Epidemiology – A New Research Challenge

François Cambien, INSERM UMR S525, University Pierre and Marie Curie, Paris.

Genomic epidemiology investigates the variability of the genome and of its products - mRNA, proteins - in large groups of individuals, in relation to diseases and disease-related phenotypes with the objective to discover patterns of variation that are associated with the occurrence and evolution of disease. Traditionally, typical epidemiological studies in the field of cardiovascular disease were dealing with a few thousands of individuals in whom a few hundreds of variables were measured. The present possibility to explore genetic variability on a whole genome scale and to globally quantify gene products in various biological media has completely changed the perspective and raises considerable challenges for study design, quality control, data management, statistical analysis, interpretation and validation of results. A typical current approach in genomic epidemiology is the Genome Wide Association (GWA) study. A series of GWA studies are currently conducted by the Welcome Trust Case-Control Consortium (WTCCC) in the UK; thousands of individuals having different major common diseases are explored using arrays which allow to genotype 500.000 single nucleotide polymorphisms in parallel. Here the statistical analysis mainly consists in performing as many independent tests as there are markers, ranking the markers and replicating the findings in independent studies to provide associations that are well validated. Several success stories already prove that the approach is valid and given the number of current ongoing projects we can anticipate several important discoveries in the years to come. GWA studies are specifically aimed at identifying “marginal” associations, but we know that the diseases we are interested in are multifactorial, involving genetic and non-genetic contributing factors and interaction among them. Acknowledging this fact raises considerable challenges that are unlikely to be solved by the huge sample size of some ongoing initiatives and by computer power. System genetics will integrate genomic data with available knowledge formalized in databases, for example in the form of ontologies, and will model interaction among sets of interconnected genetic and non-genetic factors. From the phenotype perspective, pilot studies have shown that it is now possible to explore the transcriptome of circulating cells at an epidemiological scale and this will also be the case for the plasma proteome in the near future. Very strict protocols need to be applied to reduce experimental error, especially for multicenter studies. In the last 2 years the number of genotypes that can be assayed in a typical study has been multiplied by thousands and the number of potential phenotypic measurements has been multiplied by several hundreds. It is still difficult to foresee the consequences of this change of scale from a data management and analysis perspective. It

is however certain that many previously used approaches will be useless. Hopefully, this new wealth of data may provide important new insights into the mechanisms of complex diseases.

Circulating Endothelial Cells and Microparticles as Biomarkers of Endothelial Dysfunction in Cardiovascular Disorders.

Françoise Dignat-George, INSERM UMR 608, Laboratoire d'Hématologie et d'Immunologie, UFR de Pharmacie, Marseille, France

Research for the last ten years evidenced that more than a basic monolayer, the endothelium can be viewed as a dynamic tissue, in equilibrium with endothelial derived components detectable in blood , resulting from activation and apoptosis of the vascular tree. Indeed, these deleterious processes are accompanied by profound morphological changes such as remodelling of membrane phospholipids leading to microparticle release or endothelial cell detachment resulting from loss of cell matrix interactions. Consequently, detection of circulating endothelial cells (CEC) and endothelial microparticles (EMP) have been proposed as alternative approaches to evaluate, in a non invasive way, stress, dysfunction and death of the vascular lining. This presentation will focus on the role of CEC and EMP as biomarkers for cardiovascular disorders but also as bioactive vectors contributing to the acquisition of thrombotic and inflammatory phenotypes in the vascular compartment.

Detectable at low levels in the blood flow of healthy individuals, elevated levels of CEC and EMP are detectable in vascular atherothrombotic disorders. In these pathological settings, elevation of CEC and EMP are associated with most of the cardiovascular risk factors and appear to be indicative of poor clinical outcome. In addition to be an objective marker of endothelial damage, CEC and EMP constitute a reservoir of bioactive effectors at the crossroad of atherothrombotic processes by exerting direct effects on vascular blood cells Under pathological circumstances, they support cellular cross-talk leading to vascular inflammation and tissue remodelling, endothelial dysfunction leukocyte adhesion and activation.

CEC and EMP are both markers and mediators of cardiovascular disorders with potential prognostic interest. Therefore, their measurement in blood is of potential interest in patients that are at risk for cardiovascular events. Conversion of this potential into a reality will necessitate a standardized approach to the detection and characterization of CEC and EMP, a step that will obviously increase our knowledge on their release, function and clearance.

Genetics of Type 2 Diabetes in India – 'The Asian Indian Phenotype / Genotype'

Dr.V.Mohan, Dr.Radha Venkatesan & Dr.Deepa Raj, *Dr.Mohan's Diabetes Specialities Centre &* Madras Diabetes Research Foundation, ICMR Advanced Centre for Genomics of Type 2 Diabetes, Chennai, India.

India has the largest number of people with diabetes in the world-over 40 million diabetic individuals, which represents nearly 20% of total diabetes population worldwide. The Chennai Urban Population Study (CUPS) and the Chennai Urban Rural Epidemiology Study (CURES) reveals the present prevalence of diabetes in urban India to be 72% higher than that reported in 1989 [14.3% and 8.3% in 2004 and 1989 respectively]. Indians also have a greater degree of insulin resistance, despite having lower obesity rates as judged by body mass index although they have greater waist circumference. These features constitute what is called as the "Asian Indian Phenotype" and a large part of it is probably due to genetic factors.

Large population based genetic studies done by us on some of the candidate genes have shown interesting results. We have carried out genetic studies on PPAR γ gene where we

compared the frequencies of the common Pro 12 Ala polymorphism in South Indians living in Chennai with South Asians and White Caucasians living in Dallas. We demonstrated that this polymorphism which is known to be protective against diabetes in White Caucasians does not offer protection to Indians. Another genetic study on the same study groups on Plasma Cell glycoprotein PC-1 gene polymorphism K121Q, showed it was a diabetic gene in all 3 populations studied. We also observed that the Thr394Thr (G→A) polymorphism in PGC-1 gene was strongly associated with diabetes as well as body fat in Indians and this has not been reported in other ethnic groups. Further, we noted an association of insulin receptor substrate-2 (IRS-2) Gly1057Asp polymorphism with type 2 diabetes in Asian Indians particularly in the presence of obesity. Yet another important gene which is shown recently to be implicated in type 2 diabetes is the TCF7L2 gene. Our group showed that the TCF7L2 gene was associated with type 2 diabetes in south Indians, while Yajnik's group confirmed the same association in western Indians. Thus this gene seems to be replicated in all populations studied so far. Future studies of gene environment interaction and prospective studies can throw light on the increased susceptibility to diabetes in Asian Indians.

Search for Genomic Markers in Cardiovascular Diseases: Prospects and Problems

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In this presentation, I shall start with a brief overview of genetic epidemiological approaches and findings with respect to mapping genes underlying cardiovascular diseases, with particular reference to coronary artery disease. I shall then describe our approach to ascertaining families with high familial aggregation of coronary artery disease in a specific Indian ethnic group, justifying in particular the epidemiological reasons for the choice of the specific ethnic group. I shall then provide an overview of the pathway-based approach that we have adopted to screen genes that are candidates in coronary artery disease. I shall provide some results of this ongoing study in which we have been able to find SNPs that associate with coronary artery disease. Finally, I shall provide an overview of the problems that are important to overcome in genetic epidemiological studies of common, complex diseases

Insulin and Gene Regulation

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Type 2 diabetes and obesity are metabolic pathologies which result from an interaction between our nutritional environment and our genetic program. It is thus of interest to identify the key genes involved in the adaptive responses of metabolism to the quality and quantity of nutrients.

In the last decade, the transcription factor SREBP-1c has emerged as a major protein involved in the regulation of genes involved in carbohydrate and lipid metabolism in the liver but also in adipose tissue, muscle and pancreatic ß-cells [1, 2]. SREBP-1c gene transcription is activated by insulin and inhibited by glucagon. SREBP-1c is synthesized as a precursor bound to the membranes of the endoplasmic reticulum. Its mature transcriptionally active nuclear form is released from this precursor by a proteolytic cleavage process, regulated by insulin. SREBP-1c transduces the effects of insulin on gene expression and thus favors glucose utilization and glycogen synthesis as well as lipid synthesis from glucose and triglyceride storage into adipocytes (SREBP-1c is also a transcription factor favoring adipocyte differentiation). Due to its anabolic effect on genes involved in glucose and lipid

storage, SREBP-1c can thus be considered as a thrifty gene. Changes in SREBP-1 expression as well as polymorphisms in the gene have been associated with a number of pathologies linked to lipotoxicity such as hypertriglyceridemia, insulin resistance, and type 2 diabetes. Interestingly, SREBP-1c is also cleaved by a process called the "Unfolded Protein Response" or "Endoplasmic reticulum stress" which has been recently associated with the development of insulin resistance [3].

1. Eberle D, Hegarty B, Bossard, P, Ferre P & Foufelle F. SREBP transcription factors: master regulators of lipid homeostasis. *Biochimie.* 2004, 86:839-48
2. Mounier C & Posner BI, Transcriptional regulation by insulin: from the receptor to the gene.*Can J Physiol Pharmacol*. 2006, 84:713-24.
3. Ozcan U, Yilmaz E, Ozcan L, Furuhashi M, Vaillancourt E, Smith RO, Gorgun CZ, Hotamisligil GS. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. *Science*. 2006, 313:1137-40.

Biomarkers in Hypertension

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A biomarker is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Variation in biomarker levels as indicator of disease trait, either risk factor or risk marker, disease state, preclinical or clinical or the rate of disease progression as well as characterization of the distribution of the markers in people in the community and in patient samples can be tested and evaluated. A significant portion of current medical research is devoted to the pursuit of biomarkers, particularly genetic, that can be used to identify disease. Hypertension a multigenic & multifactorial disorder is a common problem worldwide; increased susceptibility to high blood pressure as one of the established risk factors of cardiovascular disease with 25-60% genetic basis has been reported in individuals carrying common variants of hypertension-candidate genes. Therefore, the global objective of looking for novel genetic biomarkers for common cardiovascular diseases is incited. Genes of the renin-angiotensin–aldosterone system (RAAS) are natural candidates for sodium homeostasis and blood pressure regulation. The role of other substantial candidate genes including ADD1, DRD1, SCNN1B, ADRB2, GNB3 and HSD11B2 etc is equally important. Our own investigation supported evidences on the role of RAAS, ADD1, NOS3, SCNN1B, ADRB2 gene polymorphisms with hypertension. Further analysis of combination of variants at different loci of genes is promising. Since we believe the genetic basis of essential hypertension is derived from the few major candidate genes affecting the other related genes in blood pressure regulation in a complex network of epitasis, the application of integrative biology approaches and related biomarkers as a tool should have a significant impact on hypertension research. It promises the identification of genes responsible for hypertension, the elucidation of genetic and molecular interactions mediating target organ pathology and novel therapeutic strategies that may lead to a cure.

Session IV: Predicting and Monitoring Diabetes

Chairpersons: Pascal FERRE (France), HPS SACHDEV (India)

Monocyte Proteomics – A Key to Understand the Increased Risk of Atherosclerosis in Type II Diabetes?

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Abstract

The risk of developing cardiovascular diseases (CVD) in patients with type 2 diabetes mellitus is 2-8 times higher than in normal individuals. The increased risk of CVD in diabetes is not completely explained by traditional risk factors such as smoking, hypertension, hypercholesterolemia and glycemia control. The fact that not all patients with diabetes develop cardiovascular complications suggests that a proportion of the susceptibility to CVD in diabetes may have a genetic basis.

Atherosclerosis is one of the major vascular complications of diabetes. The initial critical event in atherosclerosis is the adhesion of circulating monocytes onto endothelial cells. Diapedesis of monocytes into the arterial intima followed by its transformation into lipid laden macrophage foam cells is recognized as central to the development of atherosclerotic lesions. The metabolic abnormalities that characterize Type 2 Diabetes such as insulin resistance, hyperinsulinemia, increased free fatty acids and hyperglycemia have been known to cause monocyte activation and differentiation, which together with endothelial dysfunction is considered to be a primary plausible cause for accelerated rate of atherosclerosis in diabetes.

A number of questions have been intriguing both the researchers and clinicians alike such as the extent of phenotypic and molecular alterations occurring in peripheral blood monocytes in diabetes. Whether there is any change in the blood monocyte population in diabetic and non-diabetic patients with and without vascular disease? ; Whether there is any change in the life span of circulating monocytes etc?

Given the compelling evidence that Indians have an increased susceptibility for atherosclerotic cardiovascular disease and diabetes, it is pertinent to search for biomarkers to identify the cause for increased risk for CVD in Indian patients with diabetes. Determining the effects of hyperglycemia, one of the most important metabolic abnormalities characterizing diabetes, on monocytes and the subsequent role of monocyte abnormalities in the development of diabetic vascular lesions are critical to understanding the pathogenesis of atherosclerotic vascular complications of diabetes. Dissecting these pathways is expected to provide new biomarkers for identifying the increased risk for atherosclerosis in type 2 diabetes.

Recent advances in understanding monocyte biology coupled with new molecular technologies provide powerful tools for studying the function of circulating monocytes in diabetes. Appropriate topics for investigation include: (i) studies to determine how hyperglycemia alters monocyte function, including changes in gene and protein expression, (ii) studies to determine what genes modulate susceptibility of monocytes to hyperglycemia induced changes (iii) studies to understand the sequence of events in the pathogenesis of hyperglycemia-induced monocyte adhesion to endothelial cells (iv) studies to determine how vascular inflammation is altered in diabetes and (v) studies to determine the effects of insulin in monocytes at the molecular and physiologic levels.

The changes in cellular behavior during a multifactorial disease like atherosclerosis in which the gene-environment interactions play a dominant role can only be interpreted when studied on genome-wide/protein-wide scale. Even though a few proteomic analyses have been attempted in pancreas, liver, skeletal muscle, adipose tissue and the heart, there is a complete lack of comprehensive studies on protein expression profiles of monocytes in type 2 diabetes. Proteomic technologies may enable the analysis and comparison of protein expression profiles in monocytes from people with type 2 diabetes, diabetic patients with CVD and normal controls. The concept of monocyte proteomics when applied appropriately has the potential to identify protein biomarkers for increased susceptibility to atherosclerotic vascular diseases and may also help in identifying novel therapeutic targets.

Objectives: Our objective is to compare circulating monocyte membrane protein expression in patients with type 2 diabetes who developed vascular disease (coronary, cerebral or peripheral vascular disease) within 5 years of first diagnosis of diabetes with monocyte membrane protein expression in patients with diabetes who did not develop vascular disease for 10 years after first diagnosis of diabetes and those who developed vascular disease after 5 years.

Specifically, expression profiles of monocyte cell adhesion molecules namely β1-integrins (CD49d, CD29) and β2 integrins (CD11a, b, c and CD 18) and receptors for endothelial cell adhesion molecules such as ICAM-1, VCAM-1 and E- Selectin would be analyzed. The differential protein profile of these cell adhesion molecules and cell surface receptor molecules is expected to provide us a clear picture of changes and structural modifications in these molecules in patients, which may help us in the early diagnosis of vascular disease in patients with type 2 diabetes.

The Fetal Origins of Insulin Resistance and the Metabolic Syndrome

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Over the past fifteen years, a large body of studies has evidenced the relation between SGA (small for gestational age) and the increased risk of insulin-resistance, type 2 diabetes and cardiovascular diseases later in life. The first reports focused on elderly and in populations where the prevalence of diabetes is already high. The association with insulin resistance and the metabolic syndrome was later extended to young adults and to pre-pubertal children. Our research programme is based on a large community-based cohort where all subjects were carefully selected on birth data and gathers 734 SGA subjects (birth weight < 10^{th} percentile) and 886 AGA (adapted for gestational age) subjects (25°< BW <75° perc.) born 1971-85. In these adults born SGA, we have reported a number of malfunctions of the adipose tissue persisting after puberty (22 yr. old) suggesting an abnormal adipose tissue which could participate to insulin-resistance and the metabolic syndrome:

- They show an excess of fat mass, preferentially abdominal, without obesity
- Insulin action on lipolysis is reduced and FFA release is not suppressed under physiological insulin concentrations
- An excessive lipolysis in response to catecholamine was observed by micro dialysis of the abdominal adipose tissue
- Leptin levels show an impaired regulation during catch-up and are low in adults
- Adiponectin levels are low and the insulin-sensitizing action is impaired.
- Pro12Ala of PPAR γ actually enhances IR in the SGA individuals whereas it shows insulin-sensitizing effect in AGA's, attesting for a real interaction with the fetal environment. and this observation has been replicated in two independent cohorts

At the same time the different features of MS (hypertension, dyslipidemia, and impaired glucose tolerance) were manifested in these SGA subjects and were clustering around IR. However, the phenotype was mild meaning that the differences between the subjects born SGA and their pairs born adapted for gestational age (AGA) were indeed significant for all features but of low magnitude. As a matter of fact, the proportion of disorders of glucose tolerance was low but twice as high in SGA in comparison to AGA (3.8 % vs. 1.6 %) and that of MS six fold higher (2.3 % vs. 0.4 %).We hypothesize that the adipose tissue, which is a major target of fetal growth restriction, is a key-tissue responsible for the metabolic complications and that the process extends beyond the perinatal period and continues to evolve in adults.

Session V: Diabetes and Cardiovascular Diseases

Chairpersons: KARINE CLEMENT (France), D PRABHAKARAN, HPS SACHDEV (India)

Identification of Genetic Markers in Indian Population: A Systematic Chaos

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Genetic predisposition is one of the main risk factors to diabetes and cardiovascular disease. A huge effort to unravel this is being undertaken worldwide from over a decade but with little success. Identification of genetic markers in India has always been a systematic replication of the work done in other populations. Recent studies show that the most celebrated Ala12 allele of PPAR Pro12Ala polymorphism which is associated with lower risk of type 2 diabetes in various populations of world does not confer protection in Indian population. Further, the initial results from the Indian Genome Variation initiative are indicative of the fact that India is a land of diverse genetic ethnicities. The frequency of Ala12 allele varies across sub-populations of India from 0.0 to as high as 0.31. Analysis of this polymorphism in these populations shows highest heterozygosity and predominance of heterozygotes in one of the isolated population in southern India, whereas in most of the other Indian sub populations, homozygous Pro12 is the dominant genotype. Moreover, a more frequent occurrence of the Ala12 is observed in the sub-populations known to have a higher prevalence of Diabetes. Similar observations are made for C677T polymorphism of MTHFR gene that has been globally associated with many disease phenotypes including premature CAD, diabetes, neural tube defects etc. in the background of folate deficiency. The T allele of C677T polymorphism is less frequent in majority of Indian sub-populations compared to Caucasians, Chinese and Japanese that correlates well with the mortality data due to CVD from a recent survey from Registrar General of India. Given, such a picture it is time that high risk groups are identified and hunt for genetic markers are done aggressively adopting *de novo* methods and not a simple systematic replication which is silently but constantly increasing chaos in disease identification in India.

RECOMMENDATIONS OF WORKSHOP

The Workshop had two group discussions (**Roundtable : Reality Check 2007; Roundtable: Critical Paths to Biomarker Development**) and one working group (Working Group: **Identification of Disease Risk: Genetic/ Genomic Approaches**) which explored the recent advances in biomarker research and identified areas for collaboration.

The Group suggested that biomarkers are objective measures of risk, disease status, and/or health outcomes. The Indo – French collaboration under ICMR INSERM will search for and validate new biological markers – biomarkers – in cardiovascular diseases and diabetes.

The aim of this search for biomarkers will be to accelerate the delivery of successful new technologies, medicines, and therapies for prevention, early detection, diagnosis, and treatment of disease.

The participants of the workshop observed that Indo French collaboration should lead to a number of discrete projects, each devoted to biomarker discovery, its qualification/ use in targeted areas of CVD and diabetes, with the ultimate aim to improve the public health. Projects will be proposed by individual researchers and will be developed and implemented according to their scientific merit, public health need and opportunity, and availability of support and funding. Also a call for proposals in particular areas will be made jointly by ICMR INSERM.

The Group agreed that comparison of Indian and French population will help in identification of novel and established risk factors based studies. This will require a strong investment in longitudinal cohort studies yielding state of art phenotyping and genotyping data. These cohorts will help us in predicting not only risk but disease also. Since disease progression is a lifelong process, perhaps cohorts beginning with children will be required. In view of the French and Indian paradigm for cardiovascular diseases (the two populations being on opposite scale of disease), comparison of these cohorts will provide novel markers for prediction of risk and disease.

Recommendations of the workshop are as follows:

A. RESEARCH GRANTS

The participants observed that collaborations may be sought for following types of projects:

1. **Researcher oriented projects** – Here it will be up to the researchers to develop collaborative projects
2. **Call for Proposals on specific topics by ICMR INSERM** (e.g. biobanks, genome wide scans, etc.)

B. AREAS FOR COLLABORATION

(i) Establishing Biobanks for Coronary Artery Disease and Diabetes in India

It was felt that there was a need for having a very large number of samples due to the heterogeneity of the Indian population. There is an interest in undertaking studies which can provide screening, diagnostic, staging and prognostic biomarkers. The study design can vary from case control to prospective cohorts to family studies (depending upon the research question addressed).

Collaborations will be sought for following:

1. Developing a proposal (including sample size for cohorts, case control and family studies)
2. Identification of centers which can cope with DNA processing and research on a large sample size
3. Collection of human biological samples – (including whole blood, serum, plasma, urine, tissue sample including adipose tissue samples)
4. Sample retrieval systems
5. Data analysis and retrieval systems
6. Ethical, legal and regulatory concerns screening biomarkers
7. Diagnostic biomarkers
8. Staging biomarkers
9. Prognostic biomarkers
10. Unanticipated use of stored material for analysis and consent for long term use of stored samples; confidentiality issues, ownership and control of samples and information, etc.
11. Intellectual property rights and access issues

(ii) Comparative Genotype Phenotype Studies in Relation to Classical Risk Factors, Lifestyle Socioeconomic Factors in French and Indian Population

Projects to be addressed in this area include, but are not restricted to, are as follows:

a. Comparative classical and emerging risk factors, lifestyle, socioeconomic factors in French and Indian population
b. Comparative genotype phenotype studies in relation to classical risk factors, lifestyle socioeconomic factors in French and Indian population

(iii) Collaboration on Novel Techniques/ biomolecules: Search of Novel Markers

The complex nature of atherosclerotic cardiovascular diseases demands the development of novel technologies that enable discovery of new biomarkers for early disease detection and risk stratification, which may predict clinical outcome. The novel techniques/ biomolecules developed by French and Indian researchers need to be translated into new tools for the diagnosis, prevention and treatment of CVDs and diabetes. Highly reproducible, high-throughput fractionation techniques to better detect low abundant proteins from clinical sample are required. Examples include but are not restricted to:

a. Visceral Fat Gene Expression studies
b. CEC's and EMP in Cardiovascular Complications of Diabetes and Coronary Artery Disease
c. Linking classical Lp (a) particles to the microparticles
d. $sPLA_2$ & other traditional risk factors in a representative CAD and diabetic population
e. Plasma proteomics in ACS

(iv) Gene Expression Profiles in CAD and Diabetic patients
(v) Genome Wide Analysis in CAD and Diabetes
(vi) Genetics and Proteomic Studies in Foetal origin of CAD
(vii) Transcriptomics in CAD: Case Control Studies

Annexure I

ICMR INSERM Workshop

Development of Biomarkers for CVD and Diabetes"

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