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HETEROGENEITY IN DIABETES AND BETA CELLS

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Introduction

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When one first glances at a beach or desert, the sand appears homogeneous; however, on closer inspection, there is marked heterogeneity between individual grains of sand. Similarly, although diabetes has the same hallmark of hyperglycemia, it is in fact an extremely heterogeneous group of diseases. This heterogeneity was the theme of the 20th L'Institut Servier Scientific Colloquium, held in Paris in November 2021, which we had the honor to co-chair. Professor Bernard Thorens gave us insight into the topic of heterogeneity in diabetes from a scientific perspective (**Heterogeneity in diabetes: a scientist's point of view**), while Professor Miriam Cnop described her experience as a physician (**Heterogeneity in diabetes: a physician's point of view**).

Although the topics covered were varied, a common theme running through the colloquium, and highlighted by Professor Etienne Larger (**Patients at the heart of diabetes: going beyond subtype hallmarks**), was that the key driver behind diabetes research is the goal of improved patient care. Much of this research has centered on stratification, as the ability to define disease subtypes may enable us to predict disease progression, optimize treatment, and identify new predictive biomarkers and therapeutic targets. This is particularly appealing for type 2 diabetes (T2D), with its increasing prevalence[1] and poorly understood etiology.[2] Professor Andrew Hattersley (**Genetics-based stratification: a monogenic viewpoint**) outlined the clinical utility of genetic subgrouping for monogenic diabetes, and described some of the barriers to using a similar approach for T2D. He also reminded attendees that, in order to have clinical utility, any subgroup or cluster classification must be an improvement on what we can currently achieve using separate clinical features. The predicted increases in T2D prevalence vary across different geographic regions, with the highest increase expected in Africa,[1] and there is interest in identifying whether certain phenotypes of diabetes are more prevalent in different geographic regions. Professor Jean-François Gautier outlined some subtypes for which this is the case (**Diabetes in other worlds: from Africa to India**). He also briefly touched upon his group's research into the impact of migration on T2D characteristics, and alluded to promising preliminary results from a data-driven cluster analysis based on circulating immune inflammatory cells in patients with T2D.

The rate of progression from prediabetes to T2D, as well as the response to lifestyle intervention for prediabetes, varies markedly between individuals,[3] prompting researchers to investigate why this is the case. Differing fat distribution patterns can influence progression and treatment response, and Professor Hans-Ulrich Häring described evidence showing that these fat distribution phenotypes may be related to insulin action in the brain (**Diabetes and the brain**). There is also marked heterogeneity in the rate at which type 1 diabetes (T1D) develops in the genetically at-risk population.[4] Professor Roberto Mallone described the different clinical endotypes of T1D, and presented evidence suggesting that the observed heterogeneity in progression may be due to variable contributions that immune regulation and β cell vulnerability make to disease pathogenesis (**Heterogeneity of autoimmunity in type 1 diabetes**).

T2D is a key risk factor for the development of nonalcoholic fatty liver disease (NAFLD), and the relationship between the two diseases is bidirectional.[5] NAFLD is also an extremely heterogeneous disease, with marked variability in histologic presentation and rates of progression.[6,7] Globally, it has become the most common cause of chronic liver disease, and thus there has recently been a marked increase in NAFLD research.[8] This was reflected in the fact that liver damage in patients with diabetes was the focus of 3 of the 11 colloquium presentations. Professor Catherine Postic gave a presentation titled **Hepatic steatosis and insulin resistance: a complex relationship**. The reasons for the heterogeneity in NAFLD have not been fully elucidated, and Professor Dominique Valla (hepatology specialist) spoke about risk factors for, and predictors of, disease progression and mortality (**Liver damage in diabetes**). Professor Valérie Paradis discussed the pathology of NAFLD and nonalcoholic steatohepatitis (NASH), describing current systems, as well as recent developments, for assessment and diagnosis (**NASH: a pathologist's point of view**).

Professor Francis Berenbaum opened his presentation by remarking that it may seem odd to have a presentation about osteoarthritis at a diabetes colloquium; however, as he pointed out, almost 50% of patients with diabetes also have arthritis,[9] and the two diseases may in fact be independent risk factors for each other (**Diabetes and osteoarthritis: an unhealthy relationship**).

It seems that the more we discover about diabetes, the more complicated it appears, and we realize we still have much to learn. However, the key takeaway from the colloquium, as highlighted by Professor Larger, is that, no matter how much we discover about disease subtypes and etiology, there are exceptions to these patterns, and we must never lose sight of treating each patient as an individual.

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