

Editorial

THE PROGRESSES IN TYPE 2 DIABETES GENETIC ARE EXPLOSIVE, BUT WITH MINIMAL EFFECT ON THE PREDICTION OF THE DISEASE

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Diabetes mellitus is one of the diseases that can become manifest from the first up to the last day of life¹. The incidence of the disease however can vary widely between age groups: from 0,1 cases/100.000 persons/year (during the first year of life) to higher than 500 cases/100.000 persons/year (for the age group 60-70 years). Each of the various diabetes phenotypes described to date can be more frequent in a particular age group but can be encountered however (even if with lower frequency) in any age group. The only notable exception is the neonatal diabetes which, by definition has its onset in the first 6 months after birth. Gestational diabetes mellitus has also, by definition, a precise positioning but its onset depends on the age at the time of pregnancy.

If we refer only to the two major phenotypes of diabetes, known as Type 1 diabetes (T1DM) and Type 2 diabetes (T2DM), the lower frequency of diabetes in young ages is associated with a rapid process of beta cell mass destruction, clinically expressed by a shorter diagnostic period and a relatively short (months/years) pre-diagnostic period ("normo-glycemic" or "pre-hyperglycemic" diabetes). The higher incidence of diabetes in older age groups is associated with a slow or even very slow

destruction of the beta cell mass. The high incidence of diabetes after the age of 60 years suggests the intervention of a supplementary mechanism, maybe related somehow with the senescence process and reflected in amyloid deposits replacing normal cells.

With the exception of the occasional destruction of the pancreas (wider or narrower surgical resection, intoxication with different chemicals with pancreatic tropism like vacor or streptozotocin, etc.) a genetic factor in diabetes pathogenesis is compulsory, even if in particular cases its precise nature is hard to define. Even for the classic autoimmune T1DM phenotype, the genes described so far have < 50% predictive power and provide even less information on its pathogenesis. For the T2DM phenotype, the known genetic basis is much lower (perhaps below 20% or even 10%). For both two major diabetes phenotypes, the prediction of the disease based solely on the study of the genetic defects is far from being operational. In other words, even if a non-diabetic subject would carry all the known gene variants associated with T1DM, the prediction of the disease would not be possible (no one could establish exactly the predictive power that could be 70%, 60%, 50% or maybe lower). The same is

valid in T2DM, for which the predictive power is even lower (~5% or lower).

If we refer to T2DM, positivity even for all the ~20 gene variants associated to date with this phenotype cannot actually predict diabetes onset with a better power than the risk score calculated taking into account age, BMI, diabetes heredity, blood pressure, sedentary lifestyle and eventually some biochemical markers like HDL-cholesterol and triglycerides²⁻⁷. However, it should not be ignored that the current technology for genetic analysis by Genome Wide Association scanning (using Illumina or Affimetrix method for example) is predicted to identify in the near future more gene variants – SNP's associated with the different diabetes phenotypes. It is interesting to know that the GWA approach tests every gene by assessing the association of SNPs in every known gene (~100000 SNPs) or both in known genes and in the non-coding regions throughout the genome (~300000 to 1 million)⁸. By this approach is possible to identify genes with minor/moderate or even strong genetic effect that were previously unsuspected as candidates. Even if many of these will be located probably in non-coding chromosome regions and will have only minor effects on disease susceptibility, their combined / additive effect could raise the predictive power of genetic factors up to the “threshold of active diabetogenesis”⁷⁻¹⁰.

Epigenetic effects complicate even more the understanding of genetic diabetogenic mechanisms by adding the effect of some various environmental factors (nutrients or food additives, sedentary lifestyle, etc.) on the DNA synthesis or methylation. Their mechanism of action could be related to the

micro RNAs (miR) which are short (19-22 nucleotides), endogenous noncoding RNAs, which regulate gene expression by inactivating mRNAs. The result is the decrease in the production of proteins encoded by the blocked genes. In pancreatic islets, a specific miRNA is miR-375. Its over-expression affects insulin secretion, while its inhibition enhances insulin secretion. In the liver, the predominant miRNA is miR-122 which affects cholesterol and lipid metabolism. Its inhibition decrease hepatic fatty acid synthesis, increase fatty acid oxidation and by activating AMPK, reduces liver steatosis in mice¹¹. These complex processes will further complicate the understanding of the genetic of various phenotypes of diabetes.

Nuclear chromatin is the interface between genes and environment and the principal carrier of the epigenetic information. The DNA in the β cells (as in all eukaryotic cells) is wrapped around an octamer of the histone proteins named: H2A, H2B, H3 and H4. These are associated with a large array of proteins that together form a left handed solenoidal super-coil that circumnavigates the histone core 1.8 times. This structure is called *nucleosome* and is the fundamental unit of chromatin. A chromosome represents a compaction of DNA molecules of $10^5 \mu\text{m}$ length into the cell nucleus that is typically 5 to 10 μm in diameter. Compaction is made core after core¹². The chromatin “histone-code” is constantly affected by environmental stimuli such as diet, chemicals and various pathogens. These factors can alter the architecture of chromatin and gene expression both in T1DM, and in T2DM¹³. For instance, using a GWA approach, Miao et al.¹³ found

that histone H3Lysine 9 dimethylation (H3K9me2) pattern in lymphocytes and monocytes from T1DM patients is increased, influencing a large network of factors which control immunity and inflammation.

Epigenetics refers to the influence of the various patterns on histone component acting by two enzymatic modifications: acetylation and methylation, which act together to open the chromatin structure. This allows the access of various transcription factors on the promoter regions of genes. Either silencing or awaking some genes is possible. For instance, Park et al¹⁴. have shown that T2DM induced by intrauterine growth retardation is associated with silencing of the PDX1

transcription factor through demethylation of H3K4 and methylation of H3K9.

As recently has been shown, the islet β cells with all their excitable properties, derive from the successive transcription of a unique subset of genes under the control of cell-specific transcription factors and co-factors¹⁵.

The status of chromatin as “open” or active form (euchromatin) or as “closed” or inactive form (heterochromatin) depends on methylation, acetylation, phosphorylation and ubiquitination of specific amino acid residues in the NH₂-terminal histone tails (especially Lysine and Arginine). Such modifications affect the electrical charge, shape and other properties of the histone proteins, with an essential role in the regulation of transcription.

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