Editorial
THE ENDOPLASMIC RETICULUM AND DIABETES MELLITUS

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The molecular biology data accumulated during the last few years evidenced the major importance of the Endoplasmic Reticulum (ER) in the processing of proteins translated in the ribosomes as linear amino-acid chains (primary structure of proteins) that, in order to reach their final conformation (tertiary structure), must be subject to numerous *post-translational* changes. These changes involve folding, rotation and packaging, taking place following the interaction between the amino-acids of the synthesized protein and the chaperones from the ER membrane or lumen or with some specific enzymes under tight pH or ionic concentration conditions (especially for Zn^{+2} and Ca^{+2}). The last is present inside the ER in important amounts[1-3].

The majority of post-translational changes for the synthesized protein molecules take place inside the ER, a membranous structure with an immense luminal surface (~11m^2/ml of cytoplasm), placed strategically between the cell nucleus (with which it communicates through large pores) and the Golgi apparatus system of channels/vesicles/pouches[4].

Many of the amino-acid chains that are assembled in the ribosomes are folded in an interval of milliseconds/seconds according to the information contained in the amino-acid sequence of the protein molecule itself. Between the water molecules (polarized) and the electric charges of the hydrophobic or hydrophilic amino-acids occur electro-static interactions leading to a tendency for "hiding" the hydrophobic regions of the peptide inside the protein molecule, contributing to the generation of a spatial structure that favors the subsequent processing of the molecule[5]. For the secretory pro-molecules, these involve successive splitting performed by specific convertases[6].

The role of the ER is very important in the case of secretory cells, especially for the pancreatic beta cell due to its essential function in the control of the metabolic fluxes between the three main insulin-dependent cells: adipocyte, hepatocyte and miocyte, each with its particular role in this system. The *Adipocyte* functions as an energy reserve, due its ability to store high amounts of triglycerides and to release the fatty acids during the late fasting periods, when the still available glucose is burned by the brain. The control of the lipogenesis/lipolysis processes is performed by the variations of the circulating insulin levels. The *Hepatocyte* functions as the major site for intersection between the main biochemical pathways allowing the most various transformations (amino-acids ↔ glucose ↔ fatty acids), transformations that can go either way according to the quantity and quality of dietary intake and to their utilization in the various peripheral tissues. Finally the *miocyte* represents not only the most important energy consumer, but also one of the most variable.

The energy expenditure of the muscle under intense exercise conditions can be 10 times higher than the basal expenditure, reaching up to 90% of the total energy expenditure of the human body.

Insulin is the protein that regulates the function of these three tissues (adipose, liver, muscle). Insulin secretion depends on the function of the ER inside the beta cell, while the translation of the insulin signal in the specific function of the three insulin-dependent cells (adipocyte, hepatocyte and miocyte) depends on the ER from these cells[7-10]. The ER of these cells has the remarkable ability to sense the level of different circulating fuels and to adaptatively respond to their variations[3]. The amplification of the function for any of the three cells implies the up-regulation or down-regulation of the translation for some specific molecules which become fully functional only after their post-translational processing that takes place inside the ER.

The proper function of the ER depends on the presence of some specific proteins with the role of *sensor* for pressure, pH, molecular conformation or concentration for different fuels (glucose, fatty acids, amino-acids). In conditions of high functional load (for the beta cell or for any one of the other three cells of the energy system), the requirements for protein synthesis can increase significantly, leading to an increase of the speed for the transit of these molecules through the ER. However, the speed is limited by the necessity to perform the correct post-translational processing of these molecules, a process that needs time (for some molecules milliseconds, for other seconds or even minutes). The decrease of the transit interval below a critical threshold (due to the increased speed) can lead to a "molecular crowding"[11] in the ER, a phenomenon that, in extreme cases, can lead to the agglutination of the unprocessed protein molecules and blockage of the pathways for communication with the Golgi apparatus and the other cell structures. In these conditions, signals from the ER will trigger the process of cell apoptosis, a pathogenic mechanism present in any form of diabetes [5, 10, 12-18]. In order to prevent these events, the system of ER sensors will initiate the successive activation of chaperones, converting enzymes, systems for the quality control of proteins, systems for the sorting of properly processed molecules from the defect molecules, etc. The correctly processed molecules will be included in the secretory vesicles (for the pancreatic beta cells) or in different functional cell compartments (for the adipocyte, hepatocyte and miocyte). The defect molecules will be forwarded towards local proteolysis system or towards the lysosomes where they will be degraded up to the component amino-acids[19].

The full chain of events taking place inside the ER in order to maintain the normal functional regimen of this cell structure is known as the Unfolding Protein Response (UPR). This appellative suggests an activation of the molecular processing events when their folding and packaging requires a higher speed in order to prevent the molecular crowding that can be fatal for the cell [11]. This reaction involves the intervention of ER sensors, chaperones and of the multiple pathways that can restore the normal functional regimen inside the ER[2].

The main mechanisms of the UPR process can be sorted into three main categories:

(a) Attenuation of the translation processes for new protein molecules in order to prevent the molecular crowding;

(b) Increased translation of chaperones with the role of increasing the speed of protein processing;

(c) Proteolysis of the defect molecules in order to decrease the molecular crowding and to provide the "vital space" for the correct processing of protein molecules.

If the UPR reaction fails to restore the normal processing of proteins, the accumulation of defect molecules will trigger the process of cell apoptosis by activating the CHOP molecule which will enter into the cell nucleus triggering the process of regulated cell apoptosis[2].

Finally, diabetes will appear due to the progressive decrease of the beta cell mass secondary both to the increased beta cell apoptosis and decreased beta cell regeneration[20].

The main pathogenic processes that induce the decrease of the beta cell mass are the increase of proinsulin inside the beta cell and its secretory vesicles[21], and the amyloid transformation of the beta cell amylin, a strong pro-apoptotic process, responsible for most of the diabetes cases with onset after the age of 50 years[22].

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