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## Systems Biology and Age-Induced Diseases

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### Summary

Energy metabolic system dysfunction (EMSD) is the main cause of type 2 diabetes (T2D). The EMSD can be caused by different triggers; 1- The defect of the gene (s) involved in EMS such as adiponectin, leptin, and leptin receptor, 2- A disruption in the homeostatic balance between the gene/protein (s) involved in the protection and break down of lipid droplets (LDs) within adipocytes in adipose tissue (AT), 3- Gene-environment interaction induced EMSD (e.g. diet can alter the gene behaviour) and 4- The EMS functionality decreases as people age. Since there is a high structural and lipid composition similarity between LDs and plasma lipoproteins and in particular very low-density lipoprotein (VLDL) particles, it is very important to explain the link between these two particles that play an important role in the development of EMSD. All metabolic diseases such as obesity, T2D, IR, and cardiovascular metabolic disorders increase with the age because of the reduction of metabolic function efficiency. The discovery of the components responsible for premature aging or healthy aging will provide us with the possibilities to correct premature aging or extend healthy aging. In this regard, it is essential to apply Systems Biology combined with the correct question and right study design.

### Description

Energy Metabolic System Dysfunction (EMSD) is the main cause of type 2 diabetes (T2D). The EMSD can be caused by different triggers; 1- The defect of the gene (s) involved in EMS such as adiponectin, leptin, and leptin receptor, 2- A disruption in the homeostatic balance between the gene/protein(s) involved in the protection and break down of lipid droplets (LDs) within adipocytes in adipose tissue (AT), 3- Gene-environment interaction induced EMSD (e.g. diet can alter the gene behaviour) and 4- The EMS functionality decreases as people age [1-4]. Since there is a high structural and lipid composition similarity between LDs and plasma lipoproteins and in particular very low-density lipoprotein (VLDL) particles, it is very important to explain the link between these two particles that play an important role in the development of EMSD. Both particles are built up of a hydrophobic core containing lipids and in particular triglycerides (TGs) surrounded by a hydrophilic phospholipids monolayer membrane [1-4]. VLDL is the largest carrier of TGs in plasma and known as TG-enriched VLDL particles (VLDL-TG). Also, VLDL is the major supplier of Free Fatty Acids (FFAs) from circulation to adipocytes, which is meant to store energy as inactive fuel in the form of TGs in LDs. Moreover, VLDL ensures active energy for skeletal muscles and other tissues via delivery of circulated FFAs mediated by fatty acids transporters [1-5]. On the one hand, an overload of VLDL with TGs (e.g. the diet with high content of carbohydrates) leads to large VLDL particles [6], which in turn more FFAs are available for the transport to adipocytes and ultimately storage in LDs as TGs. Since high carbohydrates diet also increases the risk for Cardiovascular Diseases (CVDs), Insulin Resistance (IR) and Type 2 Diabetes (T2D), Cherkas et al. and other investigators suggested the measurement of pooled glycogen (the stored form of glucose) as both diagnostic marker and follow up therapy of these disease [7-9]. On the other hand, an overload of LDs with TGs results in the accumulation of FFAs in the intracellular space of adipocytes, which FFAs can

be transported back to the circulation with severe cardiovascular metabolic diseases as consequence. However, the mechanism behind the transport of FFAs from adipocytes to the circulation is unknown and remained to be investigated. One possible assumption can be the penetration of cell membrane via a slowly diffusion process of FFAs with plasma membrane mediated by very high hydrophobicity character of too much accumulated FFAs in adipocytes. The major differences between VLDL particles and LDs are related to their protein contents. VLDL contains proteins such as apolipoprotein B, (APOB), APOA1, APOA2, APOA-IV, APOA-V, APOC-I, APOC-II, APOC-III, and APOE, while LDs contains perilipin (PLIN), adipophilin, tail-interacting protein of 47 kDa (TIP47), fatty acid binding protein 4 (FASP4), Hormone Sensitive Lipase (HSL), Adipose Triglyceride Lipase (ATGL), S3-12 and OXPAT. LDs-associated proteins divided in two groups; one protects and other one tries to degrade LDs. Thus, a correct function of these two groups of proteins and a homeostatic balance between FFAs delivery and storage of energy in LDs ensures the stability and functionality of LDs [1-5,10-14]

One of the major consequences of EMSD is obesity, which is mainly caused by the hypertrophy of LDs in adipocytes, resulting in obese adipocytes. Of note, the overnutrition and lack of physical activity is largely responsible for the overload of energy in the form of TGs in LDs within adipocytes and hypertrophic LDs as consequences. Importantly, obesity promotes a chronic inflammatory state, which in turn it is implicated in pathophysiological states such as Insulin Resistance (IR), T2D, cardiovascular diseases (CVDs) and stroke [1-5,7-17]. As the prevalence of obesity increases, the risk of developing obesity-induced diseases increases too. These obese adipocytes, in turn, lead to the inactivation of mitochondria. Importantly, approximately 80-85% of intracellular space of these obese adipocytes is occupied by one or two huge LDs. Based on this phenomenon, it is possible to hypothesize that LDs are the main energy supplier of adipocytes and not mitochondria. In this regard, the Long Chain Fatty Acids (LCFAs) are accumulated in adipocytes and cannot be degraded into the Short Chain Fatty Acids (SCFAs), which mitochondria uses as fuel for  $\beta$ -oxidation to produce energy (Adenosine triphosphate; ATP). Thus, these obese adipocytes appeared to inactivate mitochondria. Another possibility is that the hypertrophic LDs decrease the number of mature mitochondria or disrupt the premature-mature mitochondria process.

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In such states, it may be fair to use the term “LDs are the nuclear power of the adipocytes”. All metabolic diseases such as obesity, T2D, IR, and cardiovascular metabolic disorders increase with the age because the metabolic function efficiency reduce with the age.

In general, the aging can be defined simply as “functionality reduction of biological process”. Thus, all above mentioned states could be just referred to aging or aging-related events. Of note, it is wise to discriminate between early or premature aging and normal or healthy aging. The both mentioned types of aging are individual-dependent [7-17]. The discovery of the components responsible for premature aging or healthy aging will provide us with the possibilities to correct premature aging or extend healthy aging. In this regard, it is essential to apply Systems Biology combined with the correct question and right study design.

Systems Biology will become part of both the biologist’s as well as clinician’s toolbox. In a scientifically context, Systems Biology can be referred as “the use of a combination of all techniques and knowledge (or develop novel ones) to find answer to any biological questions”. Importantly, Systems Biology is not a computational and mathematical modelling of biological systems, which is wrongly used by many scientists. This might be due to the use of bioinformatics instead of biological software-omics. In fact, computational and mathematical modelling is used to develop software and program to collect data from biomedical databases (bioinformatica) derived from scientific publications and bring them to the scientists. It must be pointed out

that bioinformatics is also a component of Systems Biology. However, computational and mathematical modelling has to be considered as one of the tools in the Systems Biology the same as genomics, proteomics and other omics or classical techniques. Since all biomedical databases are built up based on scientific publications, bio-software uses well these databases as source information, but these softwares cannot correct these databases (Figure 1).

Why is *Systems Biology* right choice of strategy to study the age-related diseases? – Still we poorly understand the fundamental mechanisms that mediate the biological and, in turn, pathological changes in the age-related diseases such as obesity and its related diseases such as T2D, cancer, neurodegenerative diseases (e.g. Alzheimer). Obesity, T2D, CVD incidences show a sharp increase in people over the age of 50-60. Also, obesity increases cardiovascular disease events via the development of T2D, disruption of plasma lipoprotein regulation, hyper- or hypo-activity of coagulation/fibrinolysis components, and/ or a mixture of energy metabolism disorders-associated diseases. The molecular basis of these age-related events is still poorly understood and represents one of the most important questions in the field. This indicates that an innovative strategy is essential to prevent, or delay age-related diseases or extend healthy aging. Systems Biology (an integrated omics approach combined with conventional technology) is right approach to find new answers here and to elucidate the biological components and participants of aging process and their effects on the age-related diseases such as diabetes, cancer and neurodegenerative

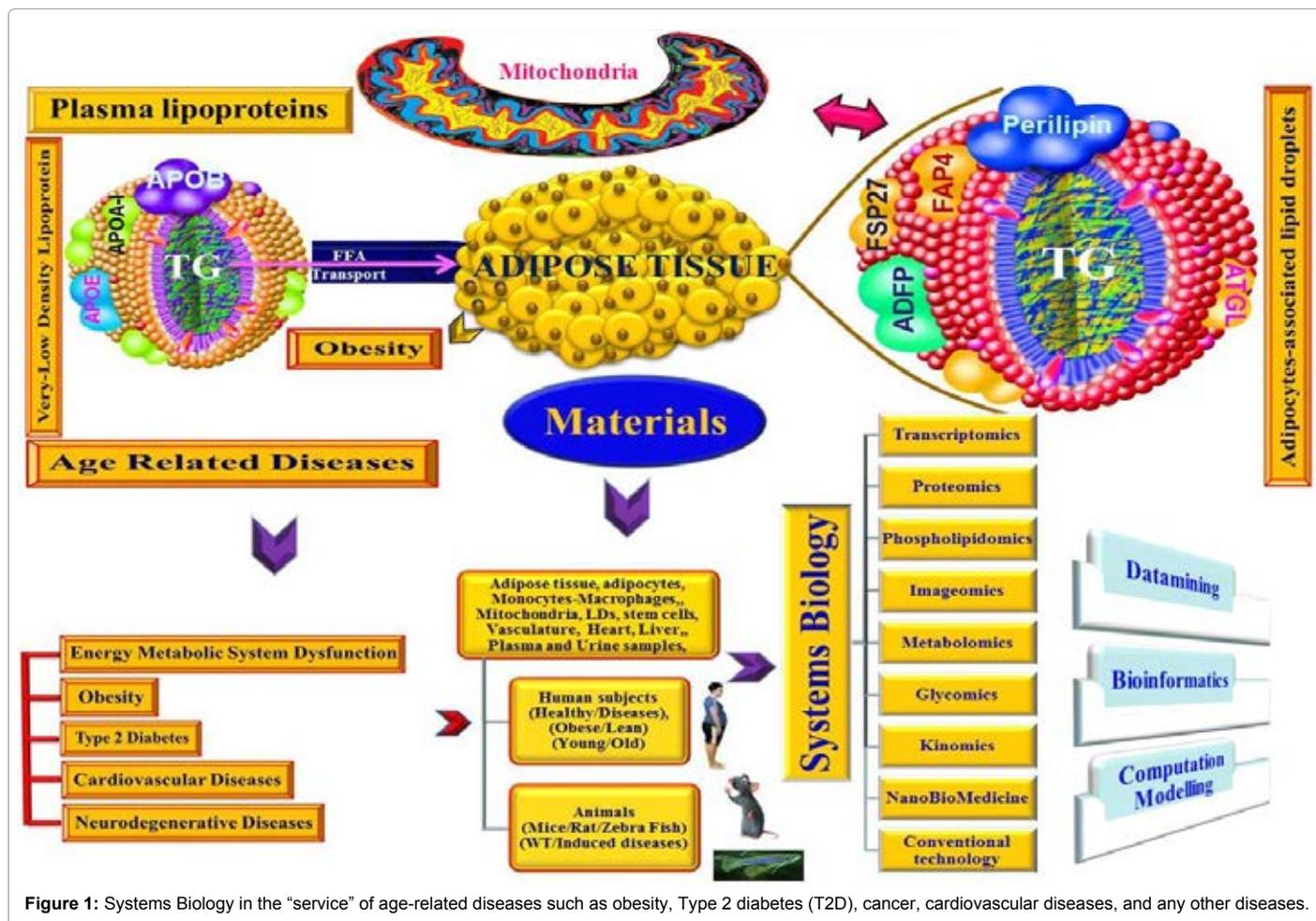


Figure 1: Systems Biology in the “service” of age-related diseases such as obesity, Type 2 diabetes (T2D), cancer, cardiovascular diseases, and any other diseases.

diseases. Of note, 'free radical theory of aging' cannot be missed in biological mechanism of ageing. Additionally, the link between mitochondria and LDs and their role in generation of free radicals in human adipocytes cannot be ignored with respect to obesity and its afflictions such as T2D and IR. As an example, Systems Biology can be applied to study "Healthy and sick" stem cells: the generation of induced pluripotent stem cells (iPSCs) derived from type 1 diabetes (T1D) and T2D patients helps us to gain more knowledge about proteome, genome and the aetiology of the diabetic disease. Although I confess that wide range of knowledge and instruments are necessary for Systems Biology approach and that cannot be ignored, the Systems Biology remained to be the right choice to study the age-related diseases. Also, Systems Biology of human preadipocytes-adipocytes helps us to understand the aetiology of obesity and diabetes and to develop novel approaches to predict, prevent and treat these metabolic diseases. At last but not least, Systems Biology will provide us with clues for developing personalised medicine for patients suffering of age-related diseases.

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