A METROLOGICAL APPROACH TOWARDS ABSOLUTE QUANTIFICATION OF PROTEIN BIOMARKERS OF METAL METABOLISM DISORDERS

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The global metabolic disorders drugs market is expected to grow from $143 billion in 2020 to $146 billion in 2021 at a compound annual growth rate (CAGR) of 2.2%. The market is expected to reach $198 billion in 2025 at a CAGR of 8% [1]. In particular, metal metabolism disorders (MMD) are those with genetic origin and, for which the functions and levels of physiologically relevant metals in the blood are controlled by specific proteins. Inherited metabolic disorders can result in protein malfunction and therefore, deficiency or toxic accumulation of metals in the body. There are several examples of MMD, of which Wilson's disease (toxic copper levels accumulate in the liver, brain, and other organs) and hemochromatosis (the intestines absorb excessive iron, which builds up in the liver, pancreas, joints, and heart) are very important with regards to metal accumulation/toxicity [1,2]. Diagnosis usually involves gene mutation testing, clinical observations and bio-chemical testing [e.g. non Ceruloplasmin (CER)-bound Cu or exchangeable Cu for Wilson's disease and total blood Fe, serum Ferritin (light chain) for hemochromatosis].

In Wilson's disease, exchangeable Cu (CuEXC) is currently measured by nephelometry as the amount of total Cu minus that of CER-bound Cu. The main limitation of this test lies in the inaccuracy of measuring CER by immunological methods not able to distinguish between the apo-CER and the active holo-CER, thus leading to biased results. In Fe disorders, Ferritin is the main storage protein for iron in tissues and is engaged in its uptake, accumulation and release in cells. The level of serum Ferritin directly reflects the level of stored iron and is normally quantified using an antibody test that detects the Ferritin protein, to diagnose iron-related disorders like hemochromatosis. For Ferritin determination, the WHO, which revised its global guidelines for the use of Ferritin thresholds in patient groups with iron deficiency and those at risk of iron overload, recognises that there is no specific recommendation on variability among analytical methods and commutability. From the foregoing account, there is an urgent need for reference methods for the quantification and identification of biochemical markers used for the early diagnosis and treatment monitoring of MMD.

This lecture will demonstrate the potential of novel Metallomic approaches based on the combination of plasma Cu protein speciation and tissue multi-element imaging to monitor both CuEXC and effects of chelating therapy in Wilson's disease patients. It will also describe first efforts to produce natural and an isotopically-enriched sulphur standards of light human ferritin towards isotope dilution quantification of such biomarker species in human serum.

[1] M. Umair, M. Alfadhel, Cells, 2019, 8, 1598.

[2] C. R. Ferreira, W. A. Gahl, Trans. Sci. Rare Diseases, 2017, 2, 101.