N-terminally truncated albumin: friend or foe of copper metabolism?

Albumin is the most abundant protein of human blood serum. The concentration of albumin in blood serum is 0.6 mM. This value is not accidental, because albumin performs important physiological functions in the human organism, such as the transport of many metabolites, drug molecules, and metal ions in the blood. Disrupting the homeostasis of albumin may have a negative effect on the physiological processes at the cellular level. Divalent copper (Cu^{II}) is one of the metals carried by albumin. Adequate delivery of copper to cells is necessary to maintain the process of oxygen respiration, by its participation in the catalytic transfer of electrons to the oxygen atom in mitochondria, which empowers the organism to acquire energy. Copper has other important roles in our body, for example Cu^{II} is part of the enzyme, superoxide dismutase, where it captures oxygen radicals that are dangerous to the body and neutralizes them to non-aggressive forms. Copper also significantly affects the transmission of nerve impulses and the level of neurotransmitters, and its deficiency may, in the worst-case scenario, cause the death of nerve cells in the brain. It also facilitates the transport and absorption of iron, and is responsible for collagen and elastin biosynthesis.

Albumin and Cu^{II} form a strong binary complex in the blood. This complex travels in the blood and reaches all cells of our body. Albumin, like every protein in the body, undergoes various modifications that have numerous effects on its functions. Modifications such as glycosylation, sulfonation and acetylation have been thoroughly investigated in terms of physicochemical properties as well as biochemical processes. In healthy people another modification of albumin is also observed. It is a truncated form, lacking the two N-terminal amino acids (short: HSA-DA). This form constitutes 2.4% of the total amount of albumin in the body. This gives us a biologically relevant 15 μM concentration of this form. What is the role of such truncated albumin? There is no answer to this question so far, as no research has been conducted in this direction, except of an unsuccessful attempt to use it as a marker of heart attack. The preliminary results that I obtained, which are the basis of this project, show that the complex of HSA-DA with Cu^{II} ions is strong. Its binding constant is similar to that of normal albumin. Preliminary studies were carried out on a model octapeptide, thanks to which it was possible to calculate the binding constant of this system, and to define for the first time its overall geometry. I discovered that the studied complex has the His-brace type structure, characteristic for a recently recognized group of LPMO enzymes, known in microorganisms and digesting cellulose. Is the structure discovered for the peptide forming in HSA-DA and what is its function? We do not know at the moment, the available literature has not described this issue. This is an intriguing question that I will try to answer in the course of my research. One possibility is that HSA-DA is involved in the regulation of copper metabolism as accessory protein for the hCtr1 receptor. Another its toxic role, for example through lipid peroxidation. To find out, it is necessary to thoroughly understand the three-dimensional structure of the Cu^{II} complex with HSA-DA, to study its interaction with the hCtr1 receptor and to test the obtained conclusions in experiments on a human cell line.

A thorough study of the catalytic activity of the model peptide with Cu^{II} will allow me to ascertain its role as a peptidic microenzyme. Following this path, I will create a randomized library of analogous peptides that may display this activity. The topic of short peptides as biocatalysts is a rapidly developing field of biotechnology. In this project, I task myself to establish whether the presence of a His-brace motif in the structure will allow to activate the catalytic properties of molecules as small as a oligopeptides and whether such peptide may be a catalyst for introduction of copper into cells? Molecule of this type would be applicable in many areas of biotechnology.

Most of the work will be performed in the Laboratory of Biological Chemistry of Metal Ions at IBB PAS. The EPR studies will be carried out in cooperation with the University of Strasbourg (France). The research results will be presented at international conferences and also published in reputable journals from the Philadelphia list.