UNIVERSITÉ DE LORRAINE

MASTER INTERNSHIP

LORRAINE Université d'Excellence

DESCRIPTION

Iron(III)-chelating model peptides as bioinspired antioxidants.

CONTEXT: Metal ions are naturally occurring in living organisms and play pivotal roles in a plenty of physiological processes, including photosynthesis, respiration, metabolism, transmission of nervous influx or even protection against pathogenic agents. Functions endorsed by the metal ions depend on their physicochemical properties such as their charge, size or electronic properties. Among the transition metal ions having an *in vivo* role, iron and copper are associated with several biological processes. Indeed, while copper is present at a trace level in the human body, it is involved as cofactor in redox enzymes (*e.g.*, galactose oxidase, superoxide dismutase) and in neurotransmission. Concomitantly, iron is essential for the respiratory chain as a key component of both hemoglobin and myoglobin.

Since metal ions play central roles in living organisms, the misregulations of their concentration, homeostasis or metabolism can trigger several pathologies. As an example, a copper overload in liver and brain is the main cause of the Wilson's disease, while a metabolic disorder of Cu(II) can be linked to the Menkes disease. In parallel, iron deficiency leads to anemia and its varying symptoms.

Usually, the transition metal ions are sequestrated by proteins and enzymes. When this is not the case, transition metal ions (such as Fe and Cu) are in their free states and can provoke significant cell damages, particularly *via* the formation of free radicals termed reactive oxygen species (or ROS). The ROS include superoxide anion radical $O_2^{\bullet-}$ and hydroxyl radical $OH^{\bullet}$ and lead to oxidative stress playing prominent roles in the development of several pathologies such as cardiovascular and neurodegenerative diseases or cancers.

In order to counteract the deleterious effects of ROS *in vivo*, living organisms have developed defense strategies involving enzymes, vitamins or proteins which regulate ROS production. Interestingly, at low concentrations, ROS contribute to the proper functioning of the organism and are needed in many vital processes, *e.g.*, in the regulation of gene expression or in the immune defense against pathogens. However, this biological ability to regulate ROS concentration depends on several factors and can be deficient, mainly due to environmental factors including smoking, food, pollution, stress, etc. This explains why the research and development of innovative antioxidants is focusing intense interests. Indeed, new effective antioxidants are expected to decrease the oxidative stress *via* a decrease of the ROS concentration. To design such antioxidants, several strategies can be considered. In this project, it is proposed to prevent the ROS formation by sequestration of transition metals involved in the Fenton and Haber-Weiss reactions.

OBJECTIVES: ROS come from the reduction of molecular oxygen O_2 *via* Fenton and Haber-Weiss reactions. In this process, reductions of O_2 to $O_2^{\bullet-}$ or of H_2O_2 to $OH^{\bullet}$ require a catalyst. Interestingly, these catalysts are transition metal ions *in vivo*, specifically copper and iron. In order to prevent the ROS formation, our strategy consists of the inhibition of the catalysis *via* sequestration of these metal ions.

Based on this context and recent results obtained by our teams, we propose for this Master course the synthesis and study of innovative chelators capable to interact with Fe(III) and presenting antioxidant activities. For the chelators, the peptide derivatives were chosen because of their indubitable qualities in terms of biocompatibility, biodegradability and high modularity. The student hired will have in charge the synthesis of a pool of peptide derivatives, the thermodynamic and structural studies of the complexation and then, the evaluation of the antioxidant properties.

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TASKS: The project is comprised of three main tasks:

#1: Synthesis. The peptide derivatives will be synthesized using solid-phase peptide synthesis, purified by reverse-phase HPLC and analyzed by ^{1}H NMR (1D and 2D), high-resolution mass spectrometry and HPLC-MS.

#2: Thermodynamic and structural studies of the complexation. The main part of this project is the study of the ability of the newly synthesized peptides to complex Fe(III), and to understand which peptide functional groups are involved in the complexation. To access the thermodynamic and structural parameters, an entire panel of analytical techniques will be carried out, including: UV-vis-NIR, FT-IR, Raman, circular dichroism, spectrofluorimetry, NMR and potentiometry.

#3: Antioxidant evaluation. Measurement of the ROS concentration will be performed indirectly by several assays, for example by measuring ascorbate consumption, H_2O_2 formation (Amplex Red test) or the formation of $OH^{\bullet}$ by spectrofluorimetry (3-CCA test).

SKILLS: The candidate should have a good knowledge in organic chemistry and in coordination chemistry.

Scientific contacts:

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The application deadline is January 13, 2020, the target start date being ***January/February 2020,*** with some flexibility on the exact start date. The internship period is 5 or 6 months with a net salary ~550 Euro/month.

HOW TO APPLY

Applications are only accepted through email. **Full CV and transcript of Master 1 records** must be sent to loic.stefan@univ-lorraine.fr and katalin.selmeczi@univ-lorraine.fr.