

Status of CIPKeBiP: Coordinator

Title of the project: **Structural insight into iodine metabolism**

Coordinator: **Prof.dr. Dušan Turk**

ARRS code: J1-7479 (F)

General information on financing

Duration: 1.1.2016 – 31.12.2018

Range of financing: 1.19 FTE

Participating research organizations

ARRS code	Research organization	Status
2990	Centre of excellence for integrated approaches in chemistry and biology of proteins, Ljubljana	Private research institution (coordinator)
0106	Jožef Stefan Institute	Public research institution
0787	University of Ljubljana, Faculty of Pharmacy	Faculty

Membership of the project team

Name	ARRS code	Research area	Position
Čurić Hrvoje	38770	Pharmacy	Researcher
Dr. Gobec Stanislav	15284	Pharmacy	Researcher
Dr. Jukič Marko	32587	Pharmacy	Researcher
Dr. Karničar Katarina	32503	Biotechnology/Microbe biotechnology	Researcher
Dr. Taler-Verčič Ajda	29544	Biochemistry and molecular biology	Researcher
Dr. Turk Dušan	04988	Biochemistry and molecular biology	Coordinator

Abstract

Iodine is the heaviest essential trace element required by the higher living organisms where it is a part of the precursor of thyroid hormones, thyroxine (T4) and its active form of triiodothyronine (T3). Thyroid hormones are responsible for the regulation of the basal metabolism of almost any cell. T3 and T4 hormones are produced in the thyroid gland. Metabolism of thyroid hormones involves selenodeiodinase. Selenium can also be found in selenoperoxidases and thyroxine, whose task is to protect the thyroid gland from hydrogen peroxide, which is necessary for the formation of thyroid hormones.

Improper function of the T3/T4 hormone results in impaired metabolism that severely decrease the quality of life, manifested as depression, weight loss, fatigue, mental problems, and may occasionally result in death. More than 10% of population is effected by thyroid disorders. Historically, most of the thyroid related disorders were the consequence of insufficient iodine uptake. In the last 30 years the WHO had issued guidelines to reduce the prevalence of thyroid hormone related disorders arising from the insufficient iodine uptake. Nowadays, however, more common cause of thyroid hormone related disorders are impaired iodine metabolism that can result in hypothyroidism (reduced hormone production) or in hyperthyroidism (increased hormone production). Hyperthyroidism is treated with thyrostatics to reduce the hormone production by inhibiting the thyroid peroxidase (TPO) or by inhibiting activation of T4 to T3 by the thyronine deiodinase (DIO). The increased TPO activity can be inhibited by carbimazole, which is converted to the active compound methimazole, or propylthiouracil. Those compounds were approved by FDA for hyperthyroidism treatment already in 1950 and 1947 and are still in use. These calls for improvements, based on new approaches and research techniques used today.

Most of the proteins involved in iodine metabolism are identified, however the few available structures provide a limited insight into their mechanism of action. Therefore we plan to provide the structural insight into the yet unknown parts of iodine metabolism and the T3/T4 hormone synthesis and processing. The crystal structures of TPO and DIOs alone will provide insight into the active site of these enzymes, whereas the complexes of inactive enzymes with their substrates or analogues will provide

insight into their reaction mechanisms. 3D structure of thyroglobulin will reveal the substrate of TPO and help us to understand the synthesis and release of the T3/T4 hormones. The gathered structural data will serve as a starting point for structural-based drug design.

We expect that the combined use of structural studies, ligand screening and chemical synthesis will enable us to gain a profound insight into the iodine metabolism. We hope that the gathered knowledge will assist us in drug discovery process targeting hyperthyroidism and hypothyroidism.

Phase of the project and its realization

We are concluding the first phase of the project and we are entering to the next one. The project has three phases.

Bibliographical references

We will start writing publications in the last year of the project.