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Transport system of vitamin B12 (Cobalamin) in delivery of therapeutic imaging B12-conjugates: Perspectives and problems

All animal cells need *cobalamin* (Cbl, vitamin B12), because Cbl-cofactors are involved in synthesis of DNA and membranes. The uptake of dietary Cbl by humans starts with the binding to a Cbl-specific capturing protein intrinsic factor, which facilitates the intestinal endocytosis. The internalized Cbl is transferred to blood and binds to the specific transporter transcobalamin, which delivers Cbl to all tissues. The specific surface receptor (CD320) renders the cellular uptake of transcobalamin–Cbl, and the endocytosed vitamin is processed to its cofactors via removal of a coordinated inactive group "X" from X– [Co^{3+}] Cbl. The Cbl-transport system is a vehicle, which guarantees a universal passage through cellular membranes for any compound attached to Cbl, nearly irrespective of its size and chemical features. Yet, modification of Cbl cannot be done at an arbitrary place.

The crystallographic analysis revealed the structural elements, where the attachment of external compounds gives the lowest impact on Cbl-binding. A number of fluorescent and radioactive Cbl-conjugates were used to visualize the main target tissues (e.g. liver, kidney, tumors). Several toxic Cbl-conjugates with an anti-cancer potential were also described in the literature, but the parallel targeting of both malicious and normal tissues would present a problem for patients. Some alternative approaches are apparently required.

Attachment of a non-removable "X"-group (in 4-ethylphenyl–[Co^{3+}] Cbl) demonstrated that such compounds behave as antagonists of Cbl, uselessly occupying the Cbl-transport system but giving nearly no gain in the active cofactors. Surprisingly, the tissue accumulation of the unprocessed anti-vitamin was also relatively low, apparently because of a continuous excretion of anti-Cbl from the cells. The overall effect might result in Cbl-exhaustion of the fast propagating cancer cells, combined with a low and revertible impact on other tissues.

Electrochemical synthesis of DNA-Cbl conjugates opened a potential to deliver therapeutic DNAs to the cells *in vivo*. The internalized DNA-Cbl is expected to be split into DNA and Cbl moieties, whereupon the antisense DNA would (i) provoke enzymatic degradation of the target mRNA, and/or (ii) block its translation. Malignant cells have distinct mRNA patterns, implying a possibility of the targeted effect with a low consequence for other tissues. Preliminary work with the "nonsense" DNA-prototypes (suitable for easy tracking) is discussed.

Speaker Biography

Sergey N Fedosov, Aarhus University, worked in different fields of science, covering biochemistry & molecular biology, enzymology & catalysis, organic & inorganic chemistry of cobalamin, synthesis of cobalamin derivatives and adsorbents, computer modeling of metabolism, and medical diagnostics. His work was critical for a number of biotechnological companies, developing pharmacological products. He is known in cobalamin community as inventor of "Fedosov factor" (the combined index of B12 status). He is (co)author of 81 publications (+3 patents) with citations of >100 (5 publications), >50 (12 publications), and the overall author-metrics index of h = 28 (Google Scholar).

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