THE ROLE OF COPPER IN TUMOR ANGIOGENESIS

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Copper metabolism is profoundly altered in human cancer and in tumor-bearing animals. The level of ceruloplasmin, the principal copper-transporting protein, increases four- to eight-fold during malignant progression, often before tumors become palpable. Serum copper levels correlate with tumor incidence, tumor burden, malignant progression, and recurrence in a variety of human cancers. Preclinical and in vitro studies have determined that copper is an important factor stimulating tumor angiogenesis. It seems reasonable that copper inhibitors (tetrathiomolybdate, penicillamine, zinc and/or low copper diet) could be good candidates for the inhibition of tumor angiogenesis.

The following topics will be discussed in this lecture:
- physiological and pathological neovascularization: vasculogenesis and angiogenesis;
- the degree of vascularization in the different tumor types;
- the monitoring of the effectiveness of antiangiogenic treatment;
- the steps of the tumor angiogenesis process (from a delivery of proteolytic enzymes from endothelial cells up to blood flow in the new tumor vessels);
- the changes in the extracellular matrix (ECM) facilitating the migration and invasion of both tumor and endothelial cells (from a secretion of chemotactic factors up to intra- and extravasation);
- the regulation of tumor angiogenesis (the importance of balance between activators and inhibitors);
- endogenous regulators of tumor angiogenesis (growth factors and their inhibitors, proteases and their inhibitors, trace elements, oncogenes, cellular signal transducing enzymes, cytokines and others);
- the role of copper in tumor progression and angiogenesis;
- the influence of copper on the activity of angiogenic growth factors;
- the mechanisms of angiogenesis control by copper;
- the inhibitors of copper in clinical trials;
- the clinical effects of copper reduction;
- penicillamine, tetrathiomolybdate and zinc – pre- and clinical studies;
- concluding remarks.