RESUME

CLOPIDOGREL, NO AND CO DONORS: INVESTIGATION OF THEIR EFFECTS ON THE INTERACTION BETWEEN PLATELETS, ENDOTHELIUM AND CANCER CELLS

The main goal of my work was to investigate antimetastatic effect of donors of vasoprotective mediators NO and CO as well as antiplatelet drug clopidogrel, applied alone or in the combination.

Investigations were carried out *in vivo* on the intravenous as well as orthotopic model of metastatic murine mammary gland cancer 4T1 and 4T1-luc2-tdTomato. Moreover, I performed *in vitro* experiments for more detailed investigation of the mechanisms of cancer cell dissemination and experiments on the blood taken from breast cancer patients.

Experiments *in vivo* showed antimetastatic activity of the combinations DETA/NO + CORM-A1 (NO + CO) as well as DETA/NO + clopidogrel (NO + clop) in both intravenous and orthotopic model. I found out that the main mechanism of antimetastatic action of these compounds is realized by the normalization of endothelial metabolism, while the inhibition of platelet activation was observed only on the early stages of tumor progression. However, higher concentrations of NO and CO were noticed to induce the opposite effect, stimulating metastasis.

Besides that, the combination of NO + CO possessed stronger antimetastatic effects rather on the earlier stages of tumor progression, successfully upregulating tumor blood perfusion, inhibiting EMT, and in *in vitro* experiments downregulating 4T1 cell adhesion and migration, while the combination of NO + clop retains its antimetastatic effect on the later stages, probably due to upregulation of NO bioavailability.

In *ex vivo* experiments the combination of NO + CO inhibited platelet aggregation in PRP obtained from human blood of the patients with metastatic breast cancer. The combination downregulated platelet activation by the reduction of platelet TGF-β release in *ex vivo* experiments.

Summarizing, both combinations applied in my investigations possess an effective antimetastatic action normalizing endothelial function. Such a therapy could have a beneficial effect combined with the traditional anticancer drugs. It could be also promising to apply investigated compounds with the drugs stimulating immune response. However, this potential beneficial action should be further investigated.