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Beta-Adrenergic Receptors (β-ARs) Expressed at Tumor Cells: Neuralgic Points When Targeted by β-blockers to Jeopardize Metastases Formation (From an Anthropomorphic View of a Tumor Cell)

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In 2005, Chédotal et al. [1] published a paper with the title "The brain within the tumor: new roles for axon guidance in cancers". They have shown that axon guidance molecules also regulate cell migration and apoptosis in normal and tumorigenic tissues and that they may act as tumor suppressors, mainly in respect to metastases formation. Metastases formation is the deadly threat of solid tumors in adults. If we might understand the cues and molecular mechanisms, which transform an otherwise sessile tumor cell into a migrating and malignant phenotype, which escapes immune surveillance and acquires the biological feature to settle in distant organs and forming metastases, then, we might be able to convert by intervention strategies an acute disease into a chronic one and achieve a substantial prolongation of life.

In 2007, a book "Neuronal Activity in Tumor Tissue" was edited by Zänker et al. [2], where outstanding contributions tried to answer the question: "Does a neuro-neoplastic synapse exist in a tumor mass?" As blood vessels and nervous structures often follow parallel trajectories within a tumor tissue, it is consequent to argue that tumor cells for the growth advantage and survival in an otherwise "unfriendly environment" and in respect to metastases formation use common cues that induce vascularization (VEGF) and innervation (neurotransmitters).

Beta-ARs are a family of G-protein coupled receptors that address multiple signaling cascades and, activating among other cellular activities, the migratory machinery, a mandatory requisite to initiate metastases formation [3]. The catecholamine stress neurotransmitters nor epinephrine and epinephrine are the physiological agonists for ß-ARs. First evidence for a regulatory role of ß-ARs and their agonists in cancer cell migration was provided and summarized by Entschladen et al. [4]. The proof-of-principle that antagonists (beta-blockers) to ARs can inhibit norepinephrine-driven metastasis development of PC-3 human prostate cancer cells was demonstrated in a BALB/c nude mice model [5]. In a retrospective, controlled and more than 10-years follow up study by Powe et al. [6] it could be figured out that women receiving concomitantly a beta-blocker therapy for hypertension in addition the conventional breast cancer therapy regimens (surgery, chemo-/radiotherapy) showed a significant reduction in breast cancer metastasis, recurrence and mortality, and a longer disease free survival. In 2011, two retrospective studies were published, confirming the results of the initial study by Powe et al. [6] that beta-blocker therapy can reduce breast cancer progression and mortality [7,8]. A comment by Ganz et al. [9] "Expanding our therapeutic options: Beta- blockers for breast cancer?" almost took away the question mark, but is demanding for further clinical studies extended to other clinical tumor entities. Ganz et al. [10] also examined the influence of beta-blockers and ACE inhibitors in respect to the risk for breast cancer recurrence and reported data from the LACE cohort. They confirmed the hypothesis that breast cancer recurrence and survival were associated with exposure to the two commonly used classes of anti-hypertensive medications. The Nottingham-Study [6] could not demonstrate a clinical advantage for ACE inhibitors. Moreover, there is one clinical report that does not support the hypothesis that ß-adrenoceptor blockers improve survival for *common cancer* [11]. However, this study focused overall on cancer patients, diagnosed with lung, breast, colorectal, prostate and pancreatic cancer, and receiving anti-hypertensive medications (ß-blockers versus other anti-hypertensive drugs). Because of the different mode of action of, e.g. ß-blockers, i) in different tumor entities, ii) in cancer initiation, iii) in cancer recurrence (local) and iv) in metastasis formation, this study has a selection bias according to the mentioned phases of a tumor disease.

Indeed for melanoma, a follow-up report of a clinical study by De Giorgi et al. [12,13] showed that ß-blockers are a new emerging treatment option for melanoma. In a Danish cohort of patients with malignant melanoma, Lemeshow et al. [14] also found that patients receiving ß--blockers retard melanoma progression.

In order to understand and interpret clinical results from the past and in the future correctly, one has clearly to discriminate, whether a signaling neurotransmitter molecule, like nor epinephrine, is an etiological factor [15,16] to initiate a number of cancers and cancer initiation may simultaneously be prevented by an antagonist (primary prevention by ß-blockers), or the metastases forming process is driven by e.g. nor epinephrine and the antagonist (ß-blocker, propranolol) inhibit the beta-adrenergic signaling by inhibition of inflammation, angiogenesis, apoptosis/anoikis [17] and/or cell motility and trafficking [18], a mandatory cellular feature to form metastases. Thereby, the pharmacological intervention with ß-blockers reduces the capability and rate of a solid tumor to metastasize (tertiary prevention).

Moreover, it could be recently demonstrated in an *in-vitro* Matrigel assay and in an *in-vivo* orthotopic xenograft model for triple-negative breast cancer cells that propranolol and chemotherapy together resulted in synergistic, additive or antagonistic effects on cell proliferation inhibition and the combination increased significantly the survival benefit in the nude mice model [19].

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In conclusion, laboratory *in-vitro* and *in-vivo* models clearly indicate that nor epinephrine-driven metastasis formation can by inhibited by ß-blockers for different tumor entities, like breast and prostate cancer. Epidemiological studies are strongly supporting the hypothesis that ß-blockers (e.g. propranolol) applied concurrently with standard therapies for breast cancer improve the outcome of breast cancer patients. These results – from bench to bedside – are providing a strong rationale to use ß-blockers in a personalized setting for breast cancer treatment and in prospective clinical studies in order to focus on the potential of a new therapeutic medication/indication for these well-known drugs albeit to improve the clinical outcome in breast cancer and other tumor entities.

In order to address in a pharmacological setting the use of ß-blockers in oncology, it is of highly interest and it is mandatory to meet stringent criteria of personalized medicine, namely to genotype the patients for CYP2D6 allelic variations, to estimate the activity of the main metabolic pathways for ß-blockers and tamoxifen – lack, or slow, intermediate or fast metabolizer (manuscript in preparation).

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