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Isolation and characterization of circulating tumor cells (CTCs) in triple negative breast cancer patients in response to chemotherapy

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Circulating tumor cells are considered as a liquid real time biopsy. Their phenotype is not always in concordance with the primary tumor due to cancer evolution. Therefore their characterization is critical before and after therapy in order to determine the response to therapy. Our results on CTCs have shown that CTCs phenotype can change in response to standard chemotherapy. Particularly blood samples from 55 early Triple negative breast cancer patients (TNBC) was examined before and after adjuvant chemotherapy. The expression of Cytokeratins (CK), Estrogen Receptor (ER), Progesterone Receptor (PR), EGFR and HER2 on CTCs was assessed using double immunofluorescent experiments and ARIOL analysis. Our results revealed that CTCs were detected in 39 out of 55 (70.9%) patients with early TNBC tumors before the initiation and in 34 out of 55 (61.8%) after the completion of adjuvant chemotherapy. The frequency of ER-, PR- and HER2-expressing CTCs was significantly reduced post-chemotherapy ($p=0.019$, $p=0.017$, $p=0.018$) while the frequency of EGFR was not altered. The percentage of ER-, PR-, HER2- and EGFR-expressing CTCs in metastatic TNBC patients was 26%, 34%, 57% and 62%, respectively. Triple staining experiments revealed that there was no co-expression of CK/EGFR/ER, CK/EGFR/PR or CK/PR/HER2 in CTCs suggesting that ER, PR and EGFR were expressed in different subclones of CTCs in TNBC patients. In conclusion a significant percentage of CTCs in TNBC patients express HER2 and EGFR before treatment, implying that these receptors could be a potential target for the limitation of metastasis. EGFR-expressing CTCs persist after adjuvant chemotherapy, suggesting that additional treatment with EGFR-targeting agents could be used post-chemotherapy to eliminate chemo-resistant CTCs.

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After 30 years of discovery of the EPR effect for tumor drug delivery, revolution cancer therapy after overcoming problems

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Cancer is the largest human burdens in health issue. However, its therapy has not really improved much even after emergence of molecular target-drugs, antibody-drugs, liposomal or polymeric micellar-drugs, etc. We proposed a new concept of cancer drugs 30 years ago using macromolecular drugs (nanomedicines). In this concept the tumor vasculature is the target, which depends on the uniquely different pathophysiology, contrary to normal, such as micro-architecture, excessive production of vascular mediators like bradykinin and NO, and impaired lymphatic clearance from tumor bed. This concept named enhanced permeability and retention (EPR) effect is the basis of tumor-selective drug delivery. This is observed for biocompatible macromolecular-drugs of >50 KDa. It covers, however, only the first step in tumor-delivery, yet it is most critical. Second step is access to tumor cells. The third step is tumor cell-uptake. In the second step, liberation of low-MW-drugs occurs from nanoparticle facilitating rapid diffusion to tumor cell-membrane. In the third step, one can utilize upregulated glucose-transporter for internalization. We developed recently polymer-(HPMA)-conjugated pirarubicin (THP) via hydrazon bond, which is more selectively cleaved in acidic tumor environment, and liberated the low MW drug which is rapidly taken up into tumor cells more than 30 x of doxorubicin. Using this conjugate our preliminary clinical results showed to be very promising. In drug-dose below toxic level, it exhibits remarkable therapeutic effect. In many solid tumors, blood vessels are frequently embolized and blood flow is hampered. To circumvent this and enhance the EPR effect, we found use of nitroglycerin and inhibitors of angiotensin converting enzyme is highly beneficial, that facilitate tumor drug-delivery 2-3 fold. The EPR effect is also observed in metastatic tumors and inflamed tissues. All in all there are more to come for nanomedicine in cancer therapy, and enhancement of EPR will be highly recommended for tumor delivery without involving serious adverse effects.

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