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Letter to the Editor

The Search of Therapeutic Target for Triple Negative Breast Cancer - An Overview on Our Attempts of Targeting Cathepsin D

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DEAR EDITOR,

I mostly worked with my laboratory on estrogen action in luminal breast cancer and studied how we could prevent and treat them [1,2]. While looking for estrogen- induced proteins secreted by breast cancer cell lines, we focussed on a major 52k protein that we identified as pro-cathepsin D deviated out from lysosomes. This 52k protein occured to be a tissue marker predictive of relapse and metastasis but not a marker of estrogen responsiveness. Cathepsin D was not correlated with any of the classical prognostic markers such as the estrogen receptor (ER) the progesterone receptor (PR), the HER2 oncogene and node invasion [3]. Cathepsin D increased tumor cells proliferation rather than invasion [4]. Anti sens RNA decreased its mitogenic activity, stimulating our attempts to use it as a therapeutic target of breast cancer [5]. As early as in 2003, we thus speculated that cathepsin D, being over expressed in ER negative breast cancers, might be a therapeutical target of triple negative breast cancer [6]. Same proposal was made thereafter by others [7]. In fact we found that this protease is also induced by growth factors [8], that it is over expressed in the MDA MB231 breast cancer cell line and independant of ER in human breast cancer tumors [3,4].

We therefore initiated several attempts to inhibit the growth of ER negative breast cancer cells, these were continued by my colleagues in Montpellier. One approach, in collaboration with organic chemists, was to inhibit this protease activity using pepstatin derivatives. This aspartyl protease inhibitor was efficient in cell free system but inefficient when tested on cells due to its hydrophobicity. We first tried to use one cathepsin D membrane receptor, the Mannose 6 phosphate receptor, to introduce pepstatin into the cells, by constructing Man6 P/ pepstatin bio conjugates [9]. These conjugates were more active than pepstatin alone. We also tested tripeptides with statin analogs able to enter cells [10]. However in both cases, the in vitro inhibition of these conjugates on the MDA/MB 231 cell line could only be obtained at high concentrations, which did not allow to test them in vivo. A new compound, JMV4463, was more efficient to vectorize cathepsin D inhibitor into the cells and to inhibit the growth of the MDA MB 231 cells in the nude mice [11]. One major interest of these results was to support the critical role of the catalytic activity of the intra cellular cathepsin D to stimulate cancer cell proliferation and tumor growth. Further work is required to specifically target these inhibitors in tumor cells allowing to test them in patients.

A quite different appoach was to develop neutralising antibodies. The first mouse monoclonal antibodies were used to titrate cathepsin D in tumor cytosol and by immuno histochemistry in order to predict both the prognosis and the response to targeted therapies [3,12]. The cath D immuno assay in tumor cytosol will be potentially usefull to predict which patient will benefit a therapy targeted to this protease.

More recently, other colleagues in the Cancer Institute of Montpellier, collaborating with immunologists have developped humanised monoclonal antibodies able to inhibit tumor growth in vitro and in vivo in rats. Some of them are active in triple negative breast cancer in the nude mice and in patient derived xenograft (PDX) [13]. Based on these preclinical studies, therapeutic assays in human are being considered.

An additional factor which might increase the agressiveness of triple negative breast cancer and to increase the efficacy of immunotherapy is to target the androgen receptor which is expressed, without the other sex steroid receptors, in apocrine tumors [14]. One group of these androgen receptor-positive tumors can be considered as triple negative cancers, when they do not express the Her2/Neu oncogene but the HER1 oncogene. The association of androgen receptor and cathepsin D expression increases the risk of relapse, suggesting that the inhibition of both androgen action via androgen antagonist and cathepsin D via neutralising antibodies might be more efficient [15].

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