

The role of HSPs in mammary neoplasms

Heat shock proteins (HSPs, stress proteins) are an ancient and evolutionarily conserved class of proteins that act as molecular chaperones guiding the normal folding, intracellular disposition and proteolytic turnover of many of the key regulators of cell growth, differentiation and survival. These functions are subverted during oncogenesis to allow malignant transformation. Being regulators of oestrogen receptor (ER), members of HSP27, HSP70 and HSP90 families have been extensively studied in human breast cancer, in which they appears to be implicated in all the cancerogenetic mechanisms (tumor cell proliferation, differentiation, invasion, metastasis, death, and tumor immune response).

Although HSPs expression in breast cancer is not particularly informative at the diagnostic level, they are effective biomarkers for carcinogenesis. Overexpression of the small heat shock protein, HSP27 is associated with increased anchorage-independent growth, increased invasiveness.

Different HSPs are coexpressed in breast cancer and in addition, certain HSPs are significantly associated with other molecules (eg, estrogen receptors, cmyc, mutated p53, Ki 67). In particular, high levels of HSP27 and HSP70, which are important molecules in the assembly and trafficking of steroid receptors, have been often associated with ER α in female breast carcinomas.

Furthermore, HSPs are implicated with the prognosis, most notably HSP70, which is correlated with poor prognosis and reduced disease-free survival. Increased HSPs expression may also predict the response to some anticancer treatments. For example, HSP27 and HSP70 are implicated in resistance to chemotherapy.

Most HSPs (HSP70 and HSP90 alfa isoform), which have demonstrated to play many important functions in the regulation of the cell cycle, by controlling the activity of several signalling proteins, specially cyclins and retinoblastoma protein (pRb), appear to be subverted in breast cancer. A high expression of HSP70 is a prerequisite for the survival of human cancer cells of various origins, furthermore, many of the proteins chaperoned by HSP90 are involved in breast cancer progression and resistance to therapy, including the estrogen receptor, receptor tyrosine kinases of the erbB family, Akt, and mutant p53. Nevertheless, many studies have to be performed to better understand how HSPs regulation is subverted in breast cancer and how HSP dysregulation affects the molecular events involved in tumor growth and malignant progression.

Treatment implication of HSPs represent a new and very promising approach in the treatment of breast cancer, particularly for those cancers that become refractory to classical hormonal therapy with anti-estrogens agents. Highly specific inhibitors of HSP90, such as geldanamycin or the geldanamycin analog 17AAG, have been identified that redirect its chaperoning activity and decrease cellular levels of the many cancer-related client proteins that depend on it for their function. HSP90 inhibitors completed five Phase I clinical trials and enters to phase II trials. The best way to exploit the novel mechanism of action of HSPs inhibitors for anticancer therapy remains to be defined, but probably involves combination with conventional cytotoxic drugs or other molecularly targeted agents.

The elevated HSPs may also provide a tempting target for immunotherapy protocols because they are able to chaperone tumor antigens and act as biological adjuvants to break tolerance to tumor antigens and cause immune killing by cytotoxic CTL and tumor regression.

Even if human and canine mammary tumors share several biochemical, clinico-pathological and epidemiological features, only few and preliminary studies on HSPs expression have

been performed in this animal specie. These studies demonstrated a significant increase of HSP27, HSP72 and HSP90 expression, as well as a significant reduction of HSP73 in comparison to normal mammary gland. In particular, HSP27 and HSP72 appeared to be strongly positive in infiltrating tumour cells of invasive stages, where HSP27 appeared to be significantly correlated with a shorter OS. HSP90 expression was high in all stages and, like HSP73, it showed an intense positivity in lymphatic emboli. These results suggest that HSP27, HSP72 and HSP90 could be involved in carcinogenesis of canine mammary gland.

This similar pattern of changes in HSPs expression to the human counterpart validate the use of the canine model to understand the molecular mechanisms of mammary carcinogenesis and to further investigate clinical and pathologic parameters with prognostic and/or therapeutic significance in these neoplasms.