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Role of the CB_2 Cannabinoid Receptor in ERBB2-Driven Breast Cancer Progression

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A large body of evidence has demonstrated that plant-derived, endogenously produced and synthetic cannabinoids exert antitumoral actions in different models of cancer, including cell cultures, xenografted animals and genetically engineered mice (Velasco *et al.*, Nature Reviews Cancer 2012). They inhibit cancer cell proliferation, adhesion, migration and induce cell death by apoptosis. However, little is known about the role of the endocannabinoid system in tumor physio-pathology. In particular, although strong evidence point to the CB_2 cannabinoid receptor as target for anti-cancer therapy, there is no information about its role in tumor generation and progression.

To shed light on this issue, we generated animals with two genetic modifications, specifically, ErbB2 overexpression directed to the mammary epithelium, which triggers the spontaneous generation of breast tumors (Guy *et al.*, PNAS USA 1992), and genetic ablation of the CB_2 cannabinoid receptor (Buckley *et al.*, Eur J Pharmacol 2000). Comparing a population of 63 wild type animals with a population of 56 CB_2 knockout littermates, we observed that the absence of CB_2 receptors produced a striking delay in tumor appearance ($p=0.026$), reduced the number of tumors generated per animal ($p=0.04$), slowed down their growth ($p=0.008$) and diminished the percentage of animals with lung metastasis ($p=0.04$). We have also observed that animals lacking CB_2 receptors present different levels of the endogenously produced cannabinoid anandamide than the corresponding wild type animals ($n=8$, $p=0.038$). Preliminary results suggest that the differences in anandamide levels between genotypes may control the general homeostasis of the mammary gland, including its oncogenic transformation and tumor progression.

Finally, we analyzed CB_2 receptor protein ($n=166$) and mRNA levels [in two public microarray databases (Chin *et al*., Cancer Cell 2006 and Bild *et al*., Nature 2006)] in human breast cancer samples. We found a direct correlation ($p=0.03$) between receptor expression and poor prognosis.

Together, these results suggest that CB_2 receptors play a pivotal role in ErbB2-driven breast tumor generation and progression.

References:

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