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Dopamine receptor type 1 (D1R) in breast cancer: Expression, signaling and therapeutic applications

Dopamine (DA) is a catecholamine which acts as a neurotransmitter in the brain and as a circulating hormone in the periphery. DA binds to five G-protein-coupled receptors, classified by their ability to increase cAMP (D1R and D2R) or decrease cAMP (D2R, D3R and D4R). We discovered D1R overexpression in breast cancer cell lines and tumors, thus identifying this receptor as a biomarker and a novel therapeutic target in breast cancer. Using tissue microarrays, D1R was overexpressed in 30% of 751 primary breast carcinomas, and was undetectable in normal breast tissue. D1R overexpression was associated with larger tumors, higher grades, node metastasis, and shorter patient survival. Unexpectedly, selective D1R agonists signal via the cGMP/protein kinase G (PKG) pathway. Activators of this pathway suppressed cell viability, inhibited cell invasion, increased chemosensitivity, and induced apoptosis in breast cancer cell lines. Fenoldopam, a peripheral D1R agonist which does not penetrate the brain, dramatically suppressed growth of D1R-expressing xenografts in two mouse models by increasing both apoptosis and necrosis. We also developed a fluorescent imaging method for D1R-expressing tumors and metastases in these mice. Ongoing studies are optimizing a positron emission tomography (PET) imaging for detecting D1R-expressing tumors in patients. In conclusion, D1R overexpression is associated with advanced disease and poor prognosis. Activation of the D1R/cGMP/PKG pathway induces apoptosis *in vitro* and causes tumor shrinkage *in vivo*. Fenoldopam, which is FDA-approved to treat acute renal hypertension, could be repurposed as a novel therapeutics for a sub-population of patients with D1R-expressing breast tumors who fail to respond to conventional treatments.

Biography

Nira Ben-Jonathan has published 175 manuscripts, edited one book, and contributed 12 chapters to textbooks and encyclopedias. She mentored 65 students, fellows and research scientists. She was awarded the NIH Research Career Development Award, was elected Fellow of the AAAS and elected Chairman of the Gordon Research Conference on Prolactin. She received the Rieveschl Award for Outstanding Scientific Research, and the Edward Merker Lectureship in Translational Endocrinology. Over the years, she served as a member on numerous study sections of the NIH, DOD and the Komen foundation, and as chairman on five NIH study sections.

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