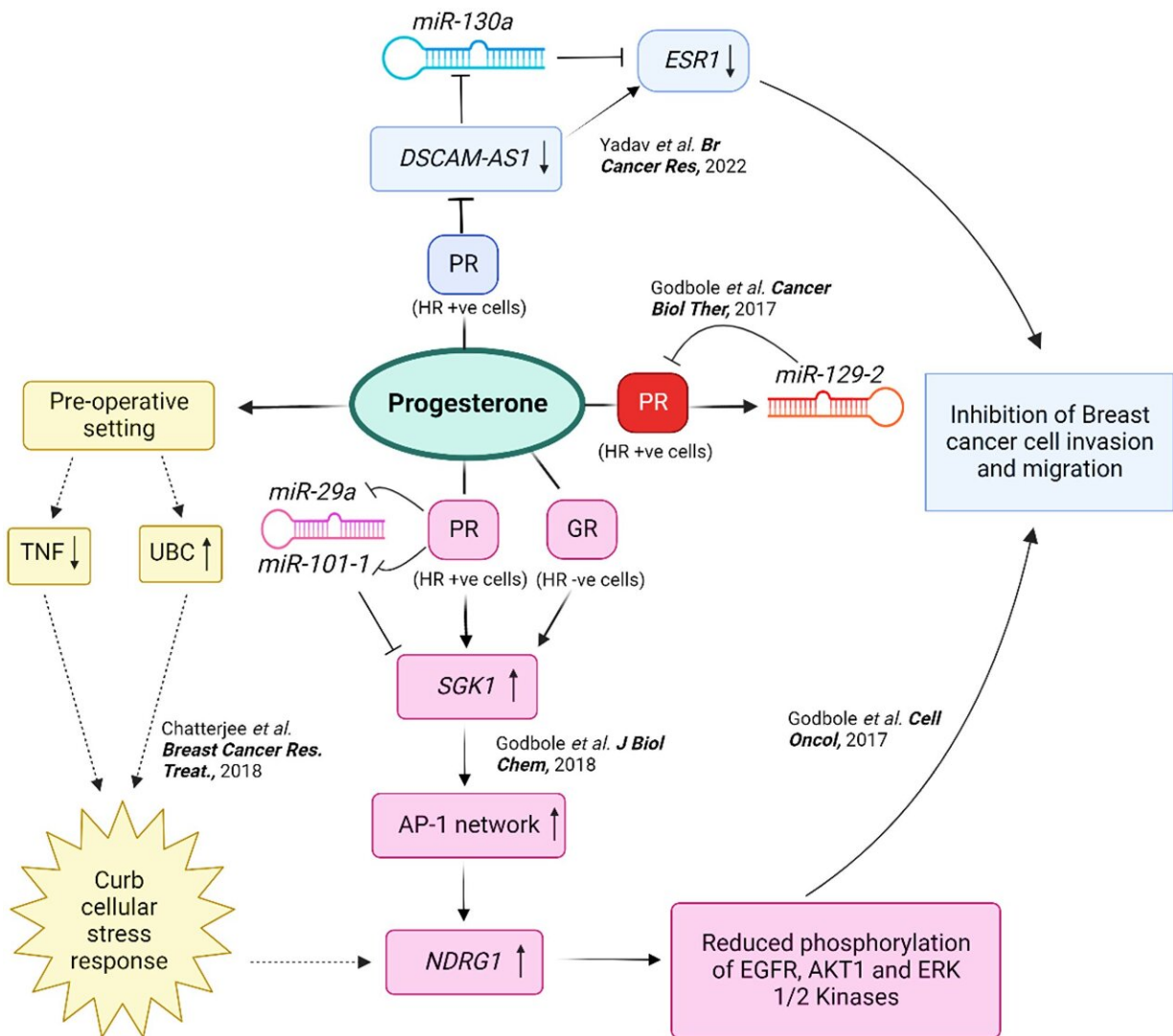


Deciphering progesterone's mechanisms of action in breast cancer

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An integrated representation of the multifaceted effects of progesterone in breast cancer. A schematic representation to describe the molecular mechanisms by which progesterone acts to curb cellular stress response and promote cell survival

in breast cancer cells. Whole transcriptomic studies (represented by dotted lines) suggest that progesterone downregulates genes involved in the inflammatory response and *TNF* production while upregulating the central node ubiquitin gene *UBC* and *N-myc downregulated gene 1*, *NDRG1*, in primary breast tumors. Thus, the effects of progesterone are mediated through a negative regulation of inflammation. Biochemical and genetic studies (represented by solid lines) suggest that progesterone treatment of breast cancer cells *in vitro* increases the expression of a *serum- and glucocorticoid-regulated kinase 1*, *SGK1*, which upregulates *NDRG1* via the *AP-1* network genes, independent of the *PR* status of the cells. Progesterone also suppresses the expression of *miR-29a* and *miR-101-1* that target the 3'-UTR of *SGK1*, reflecting a dual-regulatory mode of expression of *SGK1* in breast cancer. The increased expression of *NDRG1* reduces the phosphorylation of kinases, and thus, suppress cell invasion and migration of the cells, providing a mechanism for the previous study. Progesterone-mediated upregulation of *miR-129-2* also decreases the expression of *PR* in breast cancer. Additionally, progesterone treatment downregulates the expression of *DSCAM-AS1* in breast cancer cells that sponges *miR-130a* targeting the 3'-UTR of *ESR1*, and suppresses the migration and invasion of *PR*-positive breast cancer cells. This model provides a molecular basis for the clinical findings of preoperative progesterone intervention in breast cancer. Abbreviation: HR: Hormone Receptor. Credit: *Oncotarget* (2023). DOI: 10.18632/oncotarget.28455

A new research perspective was published in *Oncotarget*, titled "Deciphering the mechanisms of action of progesterone in breast cancer."

A practice-changing, randomized, controlled [clinical study](#) established that preoperative hydroxyprogesterone administration improves disease-free and overall survival in patients with node-positive breast cancer.

In this new perspective, researchers Gaurav Chakravorty, Suhail Ahmad, Mukul S. Godbole, Sudeep Gupta, Rajendra A. Badwe, and Amit Dutt

from Tata Memorial Centre, Homi Bhabha National Institute and MIT World Peace University summarized evidence from their studies that preoperative hydroxyprogesterone administration may improve disease-free and overall survival in patients with node-positive breast cancer by modulating cellular stress response and negative regulation of inflammation.

"This research perspective is aimed to highlight the multipronged roles of progesterone in breast cancer that underlie the associated clinical response. We also present our opinion on the role of progesterone in overcoming endocrine resistance in the patients, especially by countering the genomic effects of overexpression and mutation of ESR1 and its targets," say the researchers.

Non-coding RNAs, particularly DSCAM-AS1, play a regulatory role in this process, along with the upregulation of the kinase gene SGK1 and activation of the SGK1/AP-1/NDRG1 axis. Progesterone-induced modification of the progesterone receptor and [estrogen receptor](#) genomic binding pattern is also involved in orchestrating estrogen signaling in breast cancer, preventing cell migration and invasion, and improving patient outcomes.

The team continues on to highlight the role of progesterone in endocrine therapy resistance, which could lead to novel treatment options for patients with hormone receptor-positive breast cancer and for those who develop resistance to traditional endocrine therapies.

"Overall, while preoperative hydroxyprogesterone administration appears to be a promising strategy for improving the prognosis of patients with node-positive breast [cancer](#), the investigation of the mechanism of actions of progesterone in [breast cancer](#) remains an important area of research that holds great promise for improving patient outcomes," conclude the authors.

More information: Gaurav Chakravorty et al, Deciphering the mechanisms of action of progesterone in breast cancer, *Oncotarget* (2023). [DOI: 10.18632/oncotarget.28455](https://doi.org/10.18632/oncotarget.28455)

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