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An Anti-cancer Drug, Paclitaxel, Induces Apoptosis in MCF-7 Human Breast Cancer Cells by Generating Ceramide and Arachidonic Acid

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An anti-cancer agent, paclitaxel, is a microtubule stabilizing agent and known to arrest cells at the G_2/M of the cell cycle and apoptosis. Although much is known about its cytotoxic mechanisms, the effect of paclitaxel cannot be solely explained by microtubular interaction. Recently, several reports demonstrated that ceramide, a second messanger in apoptotic signaling, plays a key role in the nature of cellular response to anti-cancer therapies, participating in reactions to both chemotheraphy and radiation.

In this study, accumulation of ceramide mass in MCF-7 cells by the anti-cancer agent, paclitaxel, was found to occur primarily due to activation of the de novo synthesis pathway. Morever, the addition of paclitaxel resulted in the accumulation of ceramide, which was followed by a prolonged arachidonic acid release. Participation of ceramide de novo pathway in arachidonate signaling was detected since L-cycloserine, an inhibitor of de novo synthesis, was able to inhibit the paclitaxel-induced AA release and cytotoxicity. This suggest that the production of ceramide in response to paclitaxel appears to be related with in arachidonic acid release, probably cytotoxicity. Enzymatic assays revealed that serine palmitoyltransferase, the rate-limiting enzyme in ceramide de novo pathway, was activated 1.4-fold by paclitaxel treatment. An inhibitor of glucosylceramide synthesis, 1-phenyl-2-dacanoylamino-3-morpholino-1-propanol, accumulated ceramide production and increased cytotoxicity when used in combination with paclitaxel. This data suggest that activation of serine palmitoyltransferase is responsible for increased ceramide production during de novo synthesis initiated by paclitaxel and de novo synthesis may serve a specific role in arachidonic acid release.