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DRUG THERAPY

Keeping rats in the dark sheds light on tamoxifen resistance

New data from a rat model of oestrogen receptor (ER)-positive human breast cancer indicate that exposure to light at night might underlie intrinsic resistance to tamoxifen, which is a common cause of treatment failure in patients with this disease.

Circadian melatonin has been implicated as a negative regulator of breast cancer development and progression, as well as sensitivity to tamoxifen. "Thus, we hypothesized that dim light at night, by blocking the night-time rise of melatonin levels, may promote tamoxifen resistance," says Steven Hill, who was involved in the new study.

Hill and co-workers subjected rats to 12 h cycles of either light (300 lux) followed by complete darkness at 'night' (light/dark), or light then 0.2 lux dim-light exposure at night (dLEN)—mimicking a crack of light under a door in a completely dark room. MCF-7 tumour xenografts in these rats were studied before and after treatment with tamoxifen or vehicle only. "We used nude rats because, unlike many mice used in research, they have a robust nocturnal melatonin rhythm."

The team found that the rat's circadian melatonin profile was disrupted when subjected to dLEN, with low or undetectable mid-night serum levels. dLEN also increased tumour growth rates by 2.6-fold (0.73 g per day) compared with rats on the light/dark cycle. Moreover, the tumours in dLEN rats were intrinsically completely resistant to tamoxifen (growth rate: 0.69 g per day), whereas tumours regressed by 0.14 g per day after tamoxifen treatment in rats on the light/dark cycle.

"The most significant finding was that dLEN resulted in elevated expression and/or phosphorylation of key kinases and transcription factors involved in tamoxifen resistance in breast cancer." The data indicated that glucose metabolism, cAMP production and activation of cell survival and proliferation pathways, including ERα signalling, were increased in tumours as a result of dLEN.

Of note, night-time melatonin supplementation in rats subjected to dLEN evoked tumour responses similar to those observed in light/dark group, suggesting an essential role for this circadian hormone in regulating tumour growth and tamoxifen sensitivity. "These findings fit well with reports that late-night shift work increases the risk of breast cancer and that, *in vitro,* melatonin can potentiate the actions of tamoxifen on breast cancer cells."

Commenting of the potential clinical relevance of these data, Hill states that "the FDA has no guidelines on when to take tamoxifen, but just before going to bed in a completely dark room or using a sleep mask might be the ideal time." Furthermore, "patients with breast cancer who are stressed and have insomnia might be at risk of diminishing their response to endocrine therapy, and should have 8h of dark night even if they can't sleep." He concludes, "the first thing we need to do is conduct a proof-of-principle clinical trial."

David Killock

Original article Dauchy, R. T. *et al*. Circadian and melatonin disruption by exposure to light at night drives intrinsic resistance to tamoxifen therapy in breast cancer. *Cancer Res.* **74**, 1–12 (2014)