LETTER

Digoxin, HIF-1, and cancer

In a recent issue of PNAS, Zhang et al. (1) find that digoxin inhibits HIF-1 (a transcription factor highly involved in cancer development) and suggest that this effect might be observed in patients taking this drug. They also report that digoxin blocks tumor growth in mice (1). These data suggest that digoxin has anticancer potential.

The authors observe that digoxin inhibits HIF-1 at 100 nM and discuss that the therapeutic plasma concentrations of digoxin in cardiac patients are ≈10–30 nM (1). Extensive clinical use of digoxin has shown that the therapeutic plasma concentrations of this drug are 1.6 ± 1.0 nM and that higher concentrations induce toxicity because of its narrow therapeutic window (2). These data do not support the idea of HIF-1 being inhibited in patients treated with digoxin.

It has been known for some time that mouse cells are >100 times more resistant than human cells to the effects of digoxin and other cardiac glycosides (3). This means that the anticancer effects induced by digoxin in mice harboring human malignant cells (1) are probably due to interspecies differences in sensitivity and not to selective inhibition of tumor cells. Accordingly, unlike digitoxin, evidence suggests that digoxin does not inhibit the growth of cancer cells selectively (4, 5).

In brief, Zhang et al. (1) demonstrate that cardiac glycosides are a new class of HIF-1 inhibitors. However, it seems unlikely that digoxin inhibits HIF-1 at therapeutic concentrations or that the anticancer effects that they observed in mice are relevant in humans.

Miguel Lopez-Lazaro[1]
Department of Pharmacology, Faculty of Pharmacy, University of Seville, Seville 41011, Spain

1. Zhang H, et al. (2008) Digoxin and other cardiac glycosides inhibit HIF-1α synthesis and block tumor growth. *Proc Natl Acad Sci USA* 105:19579–19586.
2. Hornestam B, Jerling M, Karlsson MO, Held P (2003) Intravenously administered digoxin in patients with acute atrial fibrillation: A population pharmacokinetic/pharmacodynamic analysis based on the Digitalis in Acute Atrial Fibrillation trial. *Eur J Clin Pharmacol* 58:747–755.
3. Gupta RS, Chopra A, Stetsko DK (1986) Cellular basis for the species differences in sensitivity to cardiac glycosides (digitalis). *J Cell Physiol* 127:197–206.
4. Lopez-Lazaro M, et al. (2005) Digitoxin inhibits the growth of cancer cell lines at concentrations commonly found in cardiac patients. *J Nat Prod* 68:1642–1645.
5. Lopez-Lazaro M (2007) Digitoxin as an anticancer agent with selectivity for cancer cells: Possible mechanisms involved. *Expert Opin Ther Targets* 11:1043–1053.

Author contributions: M.L.-L. wrote the paper.

The author declares no conflict of interest.

[1]E-mail: mlopezlazaro@us.es.

www.pnas.org/cgi/doi/10.1073/pnas.0813047106