



Fast Track

Daily timed meals dissociate circadian rhythms in hepatoma and healthy host liver

Alec J. Davidson^{*†}, Martin Straume, Gene D. Block, Michael Menaker

Department of Biology, University of Virginia, Charlottesville, VA, USA

email: Alec J. Davidson (Ad2h@virginia.edu)

^{*}Correspondence to Alec J. Davidson, Department of Biology, Gilmer Hall, Box 400328, University of Virginia, Charlottesville, VA 22904-4328, USA. [†]Fax: +434-982-4505.

Funded by:

- NIA; Grant Number: F32 AG22741-01
- NSBRI; Grant Number: NCC9-58-167
- NIMH; Grant Number: RO1 MH56647, RO1 MH062517

Keywords: cancer • circadian rhythm • peripheral oscillator

Abstract

Dividing cells, including human cancers, organize processes necessary for their duplication according to circadian time. Recent evidence has shown that disruption of central regulation of circadian rhythms can increase the rate at which a variety of cancers develop in rodents. To study circadian rhythms in liver tumors, we have chemically induced hepatocellular carcinoma in transgenic rats bearing a luciferase reporter gene attached to the promoter of a core circadian clock gene (Period 1). We explanted normal liver cells and hepatomas, placed them into short-term culture, and precisely measured their molecular clock function by recording light output. Results show that isolated hepatocellular carcinoma is capable of generating circadian rhythms *in vitro*. Temporally restricting food availability to either day or night altered the phase of the rhythms in both healthy and malignant tissue. However, the hepatomas were much less sensitive to this signal resulting in markedly different phase relationships between host and tumor tissue as a function of mealtime. These data support the conclusion that hepatoma is differentially sensitive to circadian timing signals, although it maintains the circadian organization of the nonmalignant cells from which it arose. Because circadian clocks are known to modulate the sensitivity of many therapeutic cytotoxic targets, controlling mealtiming might be used to increase the efficacy of treatment. Specifically, meal and treatment schedules could be designed that take advantage of coincident times of greatest tumor sensitivity and lowest sensitivity of host tissue to damage. © 2005 Wiley-Liss, Inc.

Received: 18 July 2005; Accepted: 29 August 2005

Digital Object Identifier (DOI): 10.1002/ijc.21591

Source: <http://www3.interscience.wiley.com/cgi-bin/abstract/112125605/ABSTRACT>