Circadian Cancer Biology

The Blask & Hill Labs: A Holistic Oncology Approach

Many biological processes are affected and regulated by the circadian rhythm, which is how biological systems are able to tell time. The circadian rhythm is defined by and controlled through a central set of transcription factors (CLOCK, BMAL, PER, and CRY) with input and modulation coming from external cues – such as light exposure. Light exposure at night, which disrupts the circadian rhythm by inhibiting the synthesis of the hormone melatonin, is now recognized as a likely carcinogen. The labs of **Steve Hill** and **Dave Blask** are deciphering how melatonin signaling is important to cancer biology. They do so by focusing on melatonin and its attendant pathways, and through the use of unique models and systems.

The Central Circadian Clock and Melatonin

Science has long appreciated the importance of the circadian system to biological processes, including cancer. Normally, study of the circadian system is limited to the core clock. In mouse and rat models, the circadian system can be disrupted through exposure to bright light at irregular intervals (*i. e.* not the usual 12 light/12 dark cycle), while cells in culture can be perturbed through serum starvation or heat shock. These approaches fail to elucidate the specific pathways and processes downstream of the central clock. The link between the central circadian clock and the peripheral feedback mechanisms that can alter the circadian rhythm have not been fully described. The Blask and Hill labs address this by specifically focusing on melatonin and the individual pathways and proteins it effects. This is often done by exposing model organisms to dim light at night. This approach is unique in that it more closely mirrors what happens in humans, who are increasingly exposed to various light sources at night, disrupting melatonin production.

Melatonin Modulates Key Cancer Pathways

The Blask and Hill labs have demonstrated that melatonin can affect numerous pathways important to cancer growth, drug resistance, and metastasis. These pathways include the ERK/HER2, Akt, and Src/Kreb pathways. Unique to this lab group, they were able to interrogate not just gene expression levels as measured by qRTPCR, but levels of

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Melatonin Modulates Key Cancer Pathways (cont.)

specific proteins and their post-translational modifications. Post-translational modifications can determine if a protein is active or inactive, or mark it for degradation. These markers are regulated by melatonin, with light exposure and melatonin suppression leading to an increase in proteins with post-translational modifications that encourage cancer growth, metastasis, and drug resistance.

Unique Animal Models and Systems

The Blask and Hill labs are able to study melatonin in the context of cancer biology from the levels of individual proteins to *in vivo* study of host-cancer interactions. One of the ways that they are able to do this is through the use of unique animal models. Most laboratory mice are deficient for melatonin synthesis. However, this group utilizes the FoxA1nu mouse, which does make melatonin, to study breast cancer cells and metastasis. In these mice, normal exposure to light and darkness reduces the amount of cancer cell growth and metastasis compared to circadian-disrupted mice. Also, using a unique isolated tissue Xenograph model, this lab has studied human prostate cancer tumors perfused with human blood containing varying amounts of melatonin in rats. This model is unique in that it allows for the study of real human tumors responding to human blood with physiologically relevant levels of melatonin.

Light as a Possible Adjuvant

Melatonin has clear importance in the basic biology of cancer. Recently, preliminary data from the Blask and Hill labs demonstrates that both mice and rats exposed to artificial light that more closely mimics natural sunlight have stronger melatonin production than those exposed to conventional fluorescent lighting. This, coupled with the data implicating melatonin signaling in key cancer-relevant pathways, could mean that light itself could play a key role in the development of cancer treatments or treatment protocols. By optimizing the time of therapeutic agent delivery with the light/melatonin cycle, treatment regimens could be made more effective. It is this kind of research, linking basic biology, specific pathway interrogation and protein target analysis, and *in vivo* studies, that the Blask and Hill labs specialize in.

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