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Circadian/melatonin disruption by dim light at night drives human epithelial breast cancer to a metastatic phenotype

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Cancer patients with disrupted 24-hour (circadian) rhythms are reported to have poorer survival as compared to those with normal rhythms. We have reported that circadian/melatonin (MLT) disruption by exposure to dim light at night (dLAN) resulted in constitutive activation of ERK1/2, STAT3, and signaling nodes involved in epithelial to mesenchymal transition (EMT) in breast tumor xenografts promoting drug-resistance and that MLT can suppress the invasive activity of metastatic breast cancer. This study examined the scientific premise that dLAN-induced circadian/MLT disruption promotes EMT of epithelial MCF-7 breast tumor xenografts leading to the development of metastatic foci in the lungs, livers, and brains of circadian complete (MLT-producing) athymic nude female rats and mice. Employing athymic nude female rats and mice with ERa+ MCF-7 luciferase expressing tumor xenografts housed in LD, 12:12 (nighttime MLT) and LD, 12:12dLAN (dLAN) photoperiods or in dLAN supplemented with night time MLT, tumor from rats in dLAN showed increased growth and expression of signaling nodes involved in promoting EMT and metastasis vs. those from rats in LD: 12:12 dLAN+MLT or LD, 12:12. Nude mice exposed to dLAN showed metastatic outgrowth of MCF-7Luc xenografts forming identifiable metastatic foci in the lungs, livers, and brains of all mice, which was inhibited by MLT, as measured by IVIS small animal imaging system. CRISPR knock out of the MT1 MLT receptor in MCF-7 breast cancer cells induced a 9-fold increase in invasion as compared to parental control cells. This study is the first to show that circadian/MLT disruption by dLAN can drive EMT and metastasis.

Biography

Steven M Hill received his PhD from the University of Arizona School of Medicine and Postdoctoral studies under Dr William L McGuire at The University of Texas Health Science Center in San Antonio. He is a Professor in the Department of Structural and Cellular Biology, the Edmond and Lily Safra Chair for Breast Cancer Research, and then Director of the Tulane Center for Circadian Biology at Tulane University School of Medicine. He has published more than 100 peer-reviewed papers in reputed journals and has been serving on the Editorial Board of the Journal of Pineal Research and Frontiers in Endocrinology.

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