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Crosstalk between the circadian clock and cancer metabolism reveals novel anticancer strategies

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Despite epidemiological data indicate a close relation between circadian disruption and cancer, the suitability of a pharmacological modulation of the clock machinery as a viable approach to cancer therapy remains to be determined. We recently obtained the first evidence that the pharmacological targeting of a circadian regulator may be a suitable anticancer strategy: we revealed that the beta-variant of circadian nuclear receptor REV-ERB, REV-ERBβ, functions as an unpredicted major regulator of clock gene expression in different human tumor tissues cells, where it plays an unexpected role in sustaining cancer cell survival when the autophagy flux is compromised. These studies also identified a novel class of compounds with a dual inhibitory activity against both REV-ERBβ and autophagy, which decreased the viability of different tumor tissue cells at concentrations from 5 to 50 times lower than the singular clinically relevant autophagy inhibitor, chloroquine. The crucial position of REV-ERB proteins in the regulation of cellular metabolism suggests the provocative hypothesis in which the inhibition of both REV-ERBβ and autophagy cooperate to induce a metabolic dysfunction that is incompatible with cancer cell viability. Consistent with this view, we obtained data indicating a REV-ERBβ-mediated transcriptional regulation of cancer metabolism. Implicit in this hypothesis is the concept that the altered circadian regulation found in several tumors may be triggered by the special metabolic needs of the cancer cell. In addition, this scenario opens the possibility that REV-ERBβ inhibition may be suitable not only for combinatorial therapy with autophagy inhibitors, but also with a number of metabolic-related anticancer drugs, which identification and optimization is source of increasing effort in cancer research.

Biography

Benedetto Grimaldi, after completing his PhD in Genetics and Molecular Biology from University of Rome, La Sapienza (Italy), transitioned into a Postdoctoral fellowship under the mentorship of Prof. Sassone-Corsi (University of California, Irvine, USA), a leader in the field of circadian clock, metabolism and epigenetics. He is Senior Researcher at the "Istituto Italiano di Tecnologia (IIT)", Italy, where he directs a laboratory of Molecular Medicine pursuing a line of research focused on the study of "clock-related pathologies", and on the identification and evaluation of novel molecules with "clock modulator" activity for therapeutic applications.

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