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Health & Medicine

Editorial on the Research Topic

Sirtuinome Rewiring to Hijack Cancer Cell Behavior and Hamper Resistance to Anticancer Intervention

Extensive reprogramming of energy metabolism and detoxification processes are increasingly seen as critical factors involved in metastatic progression and in development of chemo- and radio-resistance (1 – 3).

Mammal sirtuins (SIRT1-7) are a family of conserved NAD^+-dependent protein deac(et)ylases and/or mono-[ADP-ribosyl]transferases with varied cellular distribution. Their role as epigenetic players and crucial regulators of energy metabolism and adaptation to cellular stress is currently under extensive investigation worldwide, not only in physiological processes (e. g., in aging) but also in the pathogenesis of cardiovascular and neurodegenerative diseases, diabetes and cancer (1 , 2 , 4 – 6). In particular, sirtuin-dependent signaling is suspected to play a dual role in cell biology, on one hand protecting DNA from genomic instability and limiting the replicative potential, on the other hand inhibiting senescence and promoting survival and growth advantage (7). Interestingly, SIRT3-5 localize to mitochondria and regulate targets involved in diverse biomolecular pathways, including energy metabolism and apoptotic death (8 – 11). Such characteristics confer a great importance to sirtuins, in terms of preventive medicine and therapeutic potential in anticancer strategies.

Unfortunately, despite the broad interest in this field, results currently available are still insufficient to draw definitive conclusions about the role of the sirtuinome in the regulation of key aspects of tumor cell biology, as well

as of the interactions between cancer cells and the surrounding environment. More importantly, the key question as to whether sirtuins can be considered as tumor suppressors or oncogenic proteins remains unanswered.

In this Research Topic we collected original studies (mini)review and perspective articles that were focused on the SIRT-dependent mechanisms that underlie various tumor- and cancer-related processes, both at cellular and tissue level.

Solid tumors are often accompanied by neo-vascularization that is needed to create a highly integrated micro-ecosystem aimed at limiting both hypoxic stress and build-up of toxic tumor metabolites. As reviewed by Edatt et al. , sirtuins seem to play an important role in the regulation of the functional cross-talk between pro-angiogenic and anti-angiogenic signaling surrounding neoplasms. This is achieved by controlling proliferation and migration of endothelial cells, as well as through the direct or indirect modulation of the activity of eNOS, p53, HIF-1α, FOXO, Notch, VEGF, and other factors that are essential to vascular function and organization. The authors also provided evidence of the involvement of several key miRNAs in such a regulation. Edatt et al. gave also interesting details of the crucial cross-talk between pro-inflammatory signaling and pro-angiogenic pathways controlled by sirtuins in the tumor milieu, linking SIRT-dependent changes in NFκB signal transduction to interleukin release. The authors concluded that despite some apparent contradicting angiogenic roles seemingly played by sirtuins in tumors, the SIRT-dependent epigenetic regulation of vascular remodeling is

increasingly considered as a promising therapeutic target to limit or prevent tumor angiogenesis.

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