World Academy of Science, Engineering and Technology
International Journal of Mathematical and Computational Sciences
Vol:14, No:12, 2020

The Molecular Rationale for Steroid Based Therapy of Leukemia: Diagnostic and Therapeutic Implications

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Abstract : Glucocorticoid (GC) hormones, e.g. Dexamethasone and Prednisone, are widely used in the therapy of leukemia and lymphoma owing to their apoptogenic effect on lymphoid cells. However, the emergence of GC resistant cells during therapy is a major cause for treatment failure, urging the need for novel strategies that maintain leukemia sensitivity to the pro-apoptotic activity of GCs. GCs act by binding to the GC receptor (GR), which, in its inactive state, is sequestered in the cytosol by a multi-subunit complex of heat shock proteins. Upon ligand binding, the complex dissociates, allowing GR activation and translocation to the nucleus, where it regulates transcription of multiple genes. We demonstrated that in addition to gene expression, GR also regulates microRNA (miR) expression. Deep-sequencing analysis revealed 14 miRs that are regulated in GC-sensitive but resistant leukemias upon treatment with GC. GC up-regulates miR-103, miR-15~16 and miR-30e/d, while down-regulates miR-17, mir-18a, miR-19a, miR-19b, miR-20a and miR-92a (members of the miR-17~92a multi-cistron). Upon transfection, miR-103 confers GC apoptotic sensitivity to otherwise GC-resistant cell. Furthermore, knocking down miR-103 expression reduces the GC apoptotic response of sensitive cells. miR-103 abrogates c-Myc expression, an oncogenic transcription factor which is deregulated in many cancers. In addition, miR-103 up-regulates Bim, a pro-apoptotic protein crucial for GC-induced death. Activated glycogen synthase kinase 3 (GSK3) is also crucial for GC-induced apoptosis. GSK3 is active in GC-sensitive but not in GC-resistant cells. We found that GSK3 associates with the GR multi-subunit complex. Upon GC exposure, it dissociates from the GR and interacts with Bim to enable activation of the mitochondrial apoptosis pathway. miR-103 mediated c-Myc ablation is followed by down-regulation of the multi-cistron miR-17~92a, in particular miR-18a and miR-20a. miR-18a targets GR for degradation whereas miR-20a targets Bim degradation. Hence, miR-103 acts, in concert with Bim and GR, as a "tumor suppressor" that leads to reduced proliferation, cell-cycle arrest and cell death. We suggest that miR-103 can provide a diagnostic tool that predicts the sensitivity of leukemia to GC based therapy. Furthermore, exosomal delivery of miR-103 or up-regulation of the endogenous miR-103 could confer apoptotic sensitivity to resistant cells at the outset, thus becoming a useful therapeutic tool combined with GCs.

Keywords : apoptosis, leukemia, micro-RNA, steroids
Conference Title : ICSRD 2020 : International Conference on Scientific Research and Development
Conference Location : Chicago, United States
Conference Dates : December 12-13, 2020