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Letter to Editor

Epigenetic Modifiers as an Additive to Stem Cells Differentiation Protocols

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The process of stem cell differentiation is still a major concern for the scientists in the field. Failure to achieve complete differentiation could have a risk of abnormal development. Epigenetic repression of gene expression, through DNA methylation and/or histone deacetylation can be associated with altered or decrease response of the cells to the differentiation conditions [1]. Epigenetic modifiers are non-specific compounds that can decrease the DNA methylation, such as 5-Aza-deoxy Cytidine (5-Aza-dC) or increase the histone acetylation; e.g. Trichostatin A (TSA) and Suberoylanilidehydroxamic Acid (SAHA). We are following a protocol of serum-starving the cells for 24 hours then adding the agents daily for three consecutive days, as a prior step to the classical differentiation protocols. The differentiation is usually enhanced in an agent-specific manner. For example, 5-Aza-dC enhanced osteogenic differentiation and inhibits adipogenic differentiation of stem cells of mesenchymal origin. TSA was more efficient in enhancing chondrogenic than osteogenic differentiation. Furthermore, the cells keep their enhanced differentiation capacity, even after the cells were allowed to proliferate before starting the differentiation protocols. Such effect was evident by enhanced corresponding matrix formation when the cells were cultured as organoids [2]. In beta cell differentiation studies, SAHA and 5-Aza-dC enhanced the production of insulin. The cells pretreated with 5-Aza-dC showed 50% reduction of the global DNA methylation index after the completion of the differentiation protocol; i.e. 15 days after the exposure to the demethylating agent. These cells were more responsive to the high glucose challenge as shown by insulin secretion in the media (El-Serafi et al, in press). These data showed that the effect of these agents was specific and persistent. Ramos et al, in 2015, used and through RNAseq approach and reported that 5-Aza-dC is targeted and directed to certain genes [3]. SAHA and TSA were also targeted to a similar set of genes [4]. These findings are contradictory to the findings by Alexanian in 2007, which showed similar effect of 5-Aza-dC and TSA for the neurogenic differentiation of stem cells [5]. Furthermore, Alexanian showed additive effect of 5-Aza-dC and TSA. Our unpublished data showed mixed gene expression and matrix characteristics with the combined treatment, which suggested stimulation of different signaling pathways. As these agents are approved by the Food and Drug Agency (FDA) for certain conditions, they could have a potential for clinical use in tissue regeneration. The next step should investigate the possible role of these compounds to induce stem cell differentiation into the ultimate targets in animal models.

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