Nucleosome Remodelers in Mesenchymal Stromal Microenvironment

(Index No. 164/16/Life Sc./25)

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ABSTRACT

Multipotency (*ability to differentiate into multiple mature cell types*) governed by asymmetrical division and self-renewal capacity (*ability to replenish the stem cell pool*) through symmetrical division are the two pivotal features of stem cells which ultimately help to maintain tissue homeostasis. In addition to regenerating tissue in response to normal wear and tear, trauma or disease, resident stem cells are now also understood to actively communicate with the tissue microenvironment as well as modulate immune components via secretion of various soluble paracrine factors and cell-to-cell interaction.

One of the most widely studied multipotent stem cells is 'mesenchymal stem cells' (MSC) which was discovered in bone marrow stroma in 1960s and originally identified as the 'colony-forming unit fibroblast'. The 'stemness' is due to their trilineage differentiation potential into adipocytes, osteoblasts or chondrocytes. Some studies have shown that MSCs can also trans-differentiate into cells of ectodermal and endodermal lineages. MSCs were later named as 'mesenchymal stromal cells' because of their heterogeneous cell multipotency and fibroblast-like properties. The phenotypic profiles of both human and mouse MSCs are that they express CD29, CD51, CD73, CD90 and CD105 but not CD31, CD45 or markers of the hematopoietic lineage.

Dynamicity in epigenetic marks are known to be decisive regulatory factors in stem cell fate determination and differentiation. Investigation of epigenetic regulation of stem cell biology has mainly focused on embryonic stem cell (ESC) in past few decades but less is known about adult stem cells (AdSCs). MSCs are the most investigated AdSC population due to their enormous potential for therapeutic applications in regenerative medicine and tissue engineering. Although transcriptional regulation has been extensively investigated, little is known about the epigenetic mechanisms underlining key aspects of MSC biology.

Thus the epigenetics of MSCs is an intriguing area of investigation holding great promise for both basic and applied researches.

Recent evidences highlight importance of epigenetic regulation and their integration with transcriptional and cell signaling machinery in determining tissue resident adult pluripotent mesenchymal stem/stoma cell (MSC) activity, lineage commitment and multicellular development. Histone modifying enzymes and large multi-subunit chromatin remodeling complexes and their cell type-specific plasticity remain the central defining features of gene regulation and establishment of tissue identity. Modulation of transcription factor expression gradient *ex vivo* and concomitant flexibility of higher order chromatin architecture in response to signaling cues are exciting approaches to regulate MSC activity and tissue rejuvenation. Being an important constituent of the adult bone marrow microenvironment/niche, pathophysiological perturbation in MSC homeostasis also causes impaired hematopoietic stem/progenitor cell function in a non-cell autonomous mechanism. In addition, MSCs can function as immune regulatory cells, for instance by virtue of its regulation of TGF-β signaling. Research in the past few years suggest that MSCs / stromal fibroblasts significantly contribute to the establishment of immunosuppressive microenvironment in shaping antitumor immunity. Therefore, it is important to understand mesenchymal stoma epigenome and transcriptional regulation to leverage its applications in regenerative medicine and immune reprogramming.

The Nucleosome Remodeling and Histone Deacetylation (NuRD) complex is a multisubunit chromatin remodeling complex that couples ATP-dependent nucleosome sliding with histone deacetylase activity. Clinical trials using HDAC inhibitors like TSA, SAHA in various human and mice models of inflammatory diseases and autoimmune disorders have shown promising outcome in ameliorating the inflammatory burden. The involvement of class I HDAC complex like NuRD in regulating inflammatory response mediated by immune cells has also been well documented over the recent years. Altogether these initial findings have led us to investigate the role of NuRD complex during inflammatory response in non-immune cells like MSCs along with its possible pivotal role in MSC-driven osteogenesis which is highly connected to the inflammatory mileu present within the MSC niche.

Our findings identify Gatad2b as a positive regulator of MSC mediated inflammatory response in spite of the fact that as an integral component of NuRD it plays a role as transcriptional repressor. *Gatad2b* deficient stroma possess a molecular signature of being less immune-responsive or more immune-suppressive which determines the plasticity of its secretome. Our data showed that in variety of *in vitro* cellular model of stromal inflammation the optimal *Gatad2b* response was in between 6 hours to 12 hours and this time frame

mimics the acute stage of inflammation. So *Gatad2b* might be a regulator of acute inflammation and acute inflammation promotes osteogenesis. Hence we hypothesised that NuRD might also have a role during MSC-driven osteogenesis and this was demonstrated further when *Gatad2b* deficient stroma showed impaired osteogenesis and activation of BMP/SMAD signaling.

Altogether this work might be valuable for future strategies with the aim of maintaining stroma mediated tissue homeostasis, developing anti-tumor immunity as well as treating various inflammatory diseases.

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Date : 30.03.2022

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