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Emerging Stem Cell Therapies in Mast Cell Biology

Bashit K*

Department of Molecular Biology, Genome institute of Stem cell and Developmental, Saudi Arabia

Abstract

The genesis and development of all higher creatures depend on stem cells, which are the basic building elements of life. The discovery of adult stem cells sparked a therapeutic and regenerative medicine revolution that is still continuing strong and inspired the development of novel treatments for diseases that were once considered incurable. The first instance of a successful stem cell therapy was hematopoietic stem cell transplantation, which is now often used to treat multiple myeloma and adult T-cell leukemia-lymphoma among other illnesses. The autologous transplantation of mesenchymal stem cells is used more frequently to promote the repair of mesenchymal tissue and other tissues, such as the lung and heart, and to treat a variety of illnesses, including diabetes, multiple sclerosis, and stroke. The therapeutic potential of additional adult stem cells, including those from the testicles, breast, intestinal, and inner ear, is now gaining attention. It has become clearer how the underlying epigenetic mechanisms of pluripotency and carcinogenesis work thanks to the discovery of induced pluripotent stem cells. It will be possible to create safer and more precise treatments by doing in-depth research on these epigenetic variations and the physiological changes they cause. It's been known for a long time that mast cells play a crucial and direct role in allergy and inflammatory reactions. These cells influence systemic and local allergic reactions, such as allergic rhinitis and anaphylaxis, in allergic disorders. In addition, several chronic inflammatory disorders are connected to mast cell mediators. Mast cells have a variety of healthy tasks, in addition to their roles in pathological circumstances. These include innate immunity, participation in host defence mechanisms against parasites, immune system immunomodulation, tissue healing, and angiogenesis. Mast cell biology is a field that still needs considerable research despite its growing importance in both physiological and pathological settings. This study provides evidence for the modulation of numerous biological processes in mast cells, including degranulation and endocytosis, by lipid rafts or raft components.

Keywords: Endocytosis; Pluripotency; Degranulation

Introduction

Cells from all over the world live in the complex organisms known as mammals. Cells are the fundamental constituents of all tissues and organs in an organism, from the delicately crafted inner ear to the robust femur. They resemble the individual parts of a city. To ensure the growth of functional organs, it is essential to govern each cell's identity, function, and location like the bricks in a tower. However, while structures must be planned and built, certain of the bricks in each multicellular organism can facilitate self-renewal and are typically referred to as stem cells (SCs) [1]. Embryonic stem cells (ESCs) are pluripotent progenitors with the ability to develop into cells from each of the three germ layers. These cells depend on a collection of transcription factors that control a network of genes necessary for their upkeep and expansion. The activity of Sox2, Oct4, Nanog, and Klf4 is most important for the preservation of ESCs among these transcription factors. Sox2, a member of the HMB-box family with ties to SRY, promotes Oct4 expression in order to preserve ESC pluripotency [2]. The coexpression of Oct4 and Sox2 therefore promotes the creation of binary complexes that bind to the corresponding enhancer elements for pro-regulatory function. Additionally, Oct4 interacts with other Sox transcription factors like Sox2, Sox4, Sox11, and Sox15 via Oct-Sox enhancers to co-regulate genes like Fgf4, Lefty1, Fbx15, Utf1, and Nanog. Nanog, a homeobox gene, is first expressed monoallelically in blastomeres at the 2–8 cell stage and only exhibits biallel expression in the pluripotent inner cell mass as the embryo develops [3]. Because of this, biallelic Nanog expression preserves pluripotency and is a crucial regulator of early embryonic development while monoallelic Nanog expression appears to promote differentiation. Maintaining the pluripotency of stem cells, Klf4 has been linked to differentiation and proliferation. It also works with Oct4 and Sox2 to control the expression of other genes, including Lefty1. Experiments have revealed that the overexpression of Sox2, Oct4, and Klf4 can start the reprogramming of adult differentiated cells into induced pluripotent stem cells that express Nanog, further demonstrating the significance of these transcription factors [4].

Induced Pluripotent Stem Cells

Growing interest in iPSCs has led to the discovery of other alternative techniques for creating iPSCs since the groundbreaking studies that showed the feasibility of inducing iPSCs from mouse fibroblasts using retroviral transduction in 2006. One of the first ways to create iPSCs was by transduction using retroviral and lentiviral vectors [5]. The process results in the integration of exogenous genetic material, such as the protooncogene c-Myc, in transformed iPSCs, which may increase the risk of tumorigenesis in iPSC-based therapies. Another notable drawback of these widely used protocols is the low transformation efficiency of adult cells to iPSCs (0.001-2%). Further subsequently, it has been demonstrated that fibroblasts can be converted to iPSCs using transfection of modified mRNA with an effectiveness of up to 4.4% without the need for extracellular genomic DNA integration. More study of miRNA sequences has also resulted in the discovery of the miR302/367 cluster, which, when used in conjunction with lentiviral transduction, displayed 10% effectiveness for converting fibroblasts to iPSCs. These advancements in iPSC production could result in the

***Corresponding author:** Bashit K, Department of Molecular Biology, Genome institute of Stem cell and Developmental, Saudi Arabia E-mail: k.bashit90@gmail.com

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creation of a higher throughput technology to produce stem cells that are more similar to adult stem cells and ESCs. iPSCs have a number of key benefits over ESCs when it comes to the design and research of therapies [6]. In comparison to allografts or xenografts made from ESCs, the immunological rejection risk is lower for iPSCs because they are patient-derived. Furthermore, obtaining iPSC precursors from patients is simpler than obtaining ESCs, which has its own set of challenges and ethical issues. Last but not least, iPSCs retain the ability to redifferentiate into the original cell type despite being epigenetically distinct from ESCs. Cell-specific kinds that are difficult to produce from ESCs could be created using this iPSC epigenetic memory.

Adult Stem Cell Therapies [7]

There has been some progress in confirming the safety of adult stem cell-based therapy for a number of disorders, despite the knowledge gaps in stem cell differentiation and iPSC reprogramming. This procedure is crucial because many of the genes that are activated in stem cells or thought to be helpful in triggering the development of iPSCs are protooncogenes, which raises the prospect that treatments using stem cells may put patients at an increased risk for developing cancer. For instance, the four transcription factors Sox2, Oct4, Nanog, and Klf4 that are frequently used in iPSC reprogramming have been connected to tumour treatment resistance, enhanced cancer malignancy, and carcinogenesis, and they are overexpressed in many malignancies and cancer stem cells. Additionally, by promoting iPSC generation at the expense of an increased risk of carcinogenesis, the inactivation of tumour suppressor genes like p53 demonstrates comparable effects.

Mesenchymal Stem Cells

The safety and efficacy of various stem cell therapies have been investigated in numerous researches. Adult stem cells, such as mesenchymal stem cells (MSCs) generated from bone marrow, are used in some of these fruitful investigations to test alternative restorative therapies. The ability of these cells to develop and give rise to other mesenchymal cells, including bone and cartilage cells, led to their initial description as MSCs. MSCs are a very diverse group of cells, and the subset of MSCs that can be isolated from bone marrow alone exhibits a wide range of cellular morphologies and antigen markers. As a result of their inherent immunomodulatory capabilities, human-marrow-derived MSC autografts were one of the first stem cell therapies to be successful [8]. Additional sources of MSCs include adipose and synovial tissues, peripheral blood, skeletal muscles, and neonatal tissues including the umbilical cord. The effects of osteoarthritis and osteonecrosis can be partially mediated by adipose tissue, which is a rich source of MSCs that have been used to induce the regeneration of bones and cartilage tissues in people. Adipose MSCs are favourable for usage because they may be easily collected by liposuction of adipose tissue, a minimally invasive process, and purified using established protocols. Because of this, if a patient cannot have bone marrow MSC extraction, adipose MSCs may be an option as a source of stem cells.

Hematopoietic Stem Cells [9]

Hematopoietic stem cells (HSCs) are also frequently used in experimental therapeutics, and early studies of HSC transplantation (HSCT) date back to the 1950s. HSCs are made up of an incredibly diverse population of multipotent stem cells that have the capacity to differentiate into every type of blood cell. By focusing on cells with certain expression markers, such as membrane glycoprotein Sca-1 and tyrosine kinase receptor c-Kit (CD117), and excluding cells with terminal differentiation signals, HSCs can be isolated from bone marrow cells. Leukemia and multiple myeloma are two malignancies that are most frequently treated using HSCT, along with other blood and bone marrow-related cancers. The use of HSCT has been limited to patients with life-threatening conditions due to potential problems connected to the procedure. Recent improvements in surgical methods and pharmacological regimens have improved patient survival rates and disease remission. Therefore, additional research will be necessary to improve the HSCT's safety and efficacy [10]. Particularly, a deeper comprehension of how the advantageous advantages of GVT might be boosted and distinguished from the unfavourable side effects like GVHD could result in significant advancements in the currently existing therapies.

Neural Stem Cells

A lot of attention has been paid to the therapeutic potential of neural stem cells (NSCs). According to studies, NSCs can also be produced from human iPSCs and can be extracted from the striatum, bone marrow, and NSC lines with a constant chromosomal number in mice. Furthermore, Oct4 overexpression enables the production of other cell types by reprogramming NSCs into iPSCs. However, some research has suggested that NSCs may be more susceptible to mutations brought on by culture, which may restrict their therapeutic potential. As a finding , more research should be done to determine the best in vitro growing conditions for preserving NSC genetic and epigenetic stability. These restrictions have made it necessary to primarily use animal experiments to assess the therapeutic effects of NSCs.

Endocytosis

It was discovered that proteins associated with the plasma membrane might undergo a selective rearrangement followed by internalisation when the idea of lipid rafts and the mobility of proteins in the plasma membrane first emerged. A process that is ordered in both time and space is receptor-mediated endocytosis, which includes the endocytosis of Fc RI. Crosslinked FcRI is endocytosed through clathrin-coated vesicles after activation and transported by the endosomal pathway before being eventually degraded in lysosomes. When mast cells are not stimulated, FcRI is scattered throughout the plasma membrane; however, when activated, the receptors quickly cluster and are present on the cell surface in lipid rafts in conjunction with GM1, gangliosides produced from GD1b, protein tyrosine kinase Lyn, and LAT [11].

Signal Transduction [12]

Immunoglobulin E was the first signalling complex firmly shown to incorporate lipid rafts (IgE). Although lipid rafts are now known to have a role in IgE signalling, it was previously believed that protein-protein interactions were the only basis for this process. The initial cue was provided by the discovery that, whereas FcRI is soluble in Triton X-100 in steady state, it becomes insoluble at low doses of this detergent after crosslinking. In addition, when in resting cells, FcRI is diffused across the plasma membrane; nevertheless, when activated, it quickly aggregates and is present on the cell surface along with the proteins ganglioside GM1 and GPI-anchored.

Mast Cell Development

Additionally, it appears that mast cell growth and recruitment are related to the expression of the ganglioside GD1b -galactosyl derivatives on mast cell surfaces. Previous research utilising the mAb AA4 shown that in all 23 of the rat tissues studied, the -galactosyl derivatives of the ganglioside GD1b were solely found in mast cells. But mAb AA4 also identified a population of big, poorly differentiated cells in bone marrow, which were most likely young mast cells. It was later

discovered that these cells were in fact very young mast cells [13]. Mast cells that are maturing cannot be distinguished from other cells based on their density or mAb AA4 because of their heterogeneity.

Discussion

The development of innovative regenerative gene therapies for enhanced intestinal function in patients with short bowel syndrome may result from additional research to clarify the molecular processes governing this regenerative mechanism. Another condition that might benefit from stem cell therapy is hearing loss brought on by the loss of cochlea hair cells. Inner ear stem cells have been discovered in the adult utricular sensory epithelium and the dorsal epithelium of the cochlear canal in the quest for a cure. These current investigations suggest a persistent effort to pinpoint possible stem cells for hearing restoration and the molecular regulators that control this procedure. In mice, pigs, and goats as well as other animal models, testicular stem cell transplantation has been utilised to successfully restore fertility. There were very few little cytoplasmic granules present in these cells, which were unable to be identified as mast cells using conventional cytological techniques. On the other hand, undifferentiated mast cell precursors found in the bone marrow do not express the ganglioside GD1b -galactosyl derivatives identified by mAb AA4. In very immature mast cells, these gangliosides start to be expressed on the cell surface alongside FcRI and at the same time as the beginning of the development of cytoplasmic granules. In every step of maturation, mast cells continue to express gangliosides produced from GD1b. According to these findings, the maturation and activity of mast cells are correlated with lipid rafts or raft components.

Conclusion

The area of stem cell medicine is quickly developing, yet many potential stem cell therapies are still in their infancy or are only supported by promising results from animal studies that may not necessarily transfer into effective treatments for people. Additionally, a noteworthy drawback of stem cell therapy human clinical trials is that they frequently only include a small number of participants or that the studies were completed in a short amount of time, such as a few years, which may not be sufficient to access the full risks of carcinogenesis. As a result, the results may not be reliable when extrapolated to assess the long-term security and efficacy of these treatments in a larger population. It is also crucial to remember that many stem cell therapies and clinical trials currently being used have little effect in reducing illness symptoms [14]. This is due to the fact that the majority of modern medicines only focus on one component of the disease. The application of a generic therapy to a heterogeneous patient population has been prompted by a combination of factors, including a limited capacity to diagnose the diverse underlying causes of similar disease symptoms and the lack of tests to identify the complex differences between individual patients. Therefore, to fully realise the potential of personalised stem cell therapies, better technologies to identify the specific genetic and epigenetic markers in each patient that contribute to each disease manifestation are increasingly crucial [15]. Future stem cell therapies' efficacy and safety will depend on our ability to manipulate the intracellular molecular pathways that control stem cell differentiation and to maintain genetic stability. These pathways can be altered to induce desired phenotypic changes as well as epigenetic modifications. To do this, more research must be done on the numerous genetic and epigenetic variants in what appear to be homogeneous stem cell populations, and the effects of each variation on differentiation, proliferation, and pluripotency must be quantified. There are still many raft structural and function questions to be answered in terms of mast cell biology [16]. Activation by Fc RI, morphogenesis, endocytosis, and maturation are only a few of the numerous areas of mast cell biology where lipid rafts and their components unquestionably play a part. Further investigation into the function of lipid rafts in mast cells may provide new targets for immunotherapies and disorders that involve mast cells or their mediators [17].

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Conflicts of Interest

The author has no known conflicts of interested associated with this paper.

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