ORIGINAL RESEARCH PAPER

Orthopaedics

AUTOLOGOUS BONE MARROW MONONUCLEAR CELLS (AUTOLOGOUSSTEMCELLS -AMATEUR TERM) IN AVASCULAR NECROSIS OF THE HIP: GENETIC MECHANISMS, REGENERATIVE POTENTIAL, AND CLINICAL TRANSLATION

KEY WORDS: Avascular necrosis, Stem cells, Mononuclear cells, Hip, Regenerative medicine, Core decompression, UGC, Ph.D./D.Sc.

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ABSTRACT

Avascular necrosis (AVN) of the femoral head is a progressive orthopaedic disorder resulting from compromised vascularity and osteocyte death, leading to structural collapse of the hip. Conventional management, including pharmacological interventions and surgical decompression, has limited potential for biological repair. In recent years, autologous bone marrow-derived mononuclear cells (BM-MNCs) have emerged as a promising therapeutic modality, combining the principles of stem cell biology with surgical orthopaedics. This review synthesises current evidence regarding the molecular pathogenesis of AVN, the regenerative mechanisms of BM-MNCs, and clinical outcomes from translational research. The discussion also contextualises the role of Ph.D./D.Sc. scientists, as defined under the University Grants Commission (UGC) 2009 and 2018 regulations, in advancing regenerative medicine.

INTRODUCTION

Avascular necrosis (AVN) of the femoral head is characterised by ischaemic death of osteocytes and marrow elements, culminating in subchondral collapse and disabling osteoarthritis (Assouline-Dayan et al., 2002). The disorder is associated with risk factors such as corticosteroid use, alcohol abuse, coagulopathies, and trauma (Moya-Angeler et al., 2015).

Traditional surgical methods, such as core decompression, relieve intraosseous pressure but do not replace necrotic bone with viable tissue (Mont and Hungerford, 2006). The emerging paradigm of regenerative medicine focuses on biological repair, wherein autologous bone marrow-derived mononuclear cells (BM-MNCs) are used to promote osteogenesis, angiogenesis, and paracrine modulation (Hernigou et al., 2002).

Importantly, such translational advances are attributable to the contributions of Ph.D./D.Sc. scientists trained under rigorous UGC norms. According to the 2009 and 2018 UGC regulations, the award of a Ph.D. is contingent upon coursework, conducting research, publications, preparation of thesis and external evaluation of thesis and public Viva voce, with the provisional certificate explicitly noting compliance with these standards (UGC,2009 or 2018). For pre-2009 enrolments, eligibility for academic and scientist positions is contingent upon six-point verification by university authorities (Honourable Vice chancellor/Pro Vice chancellor(Rector);Dean etc)These safeguards ensure that scientific leadership rests in the hands of rigorously trained scholars.

Definition Of A Scientist

A scientist is traditionally defined as an individual who systematically pursues knowledge through observation, experimentation, and analysis with the goal of advancing understanding in natural, medical, or applied Sciences often holding a doctoral degree (Ph.D. Or Equivalent) and contributing to the body of Scientific literature with peer reviewed Publications and citations (National Academies, 2005;UNESCO,2017)According to the University Grants Commission (UGC) regulations of 2009 and 2018, a scientist in the Indian academic context is recognised as an individual holding a doctoral qualification (Ph.D./ D.Sc.), which requires rigorous coursework, original research contributions, peer-reviewed publications, and evaluation by external experts (UGC, 2009; UGC, 2018). Globally, institutions such as the Organisation for Economic Co-operation and Development (OECD, 2015) and UNESCO (2017) emphasise that scientists must demonstrate professional expertise, critical thinking, and adherence to ethical standards in research and innovation. Thus, a doctoral degree serves as both a credential of academic competence and a marker of eligibility for conducting independent research at the highest level. This qualification ensures that contributions in fields like regenerative medicine are led by professionals trained to generate reproducible, peer-validated knowledge.

Genetic And Molecular Pathogenesis Of AVN

The pathogenesis of AVN is multifactorial, involving genetic, vascular, and cellular factors.

- Genetic predispositions: Mutations and polymorphisms in factor V Leiden, eNOS, and PAI-1 genes predispose to

microvascular thrombosis (Jones, 2015).
- Ischaemia and hypoxia: Hypoxic conditions activate hypoxia-inducible factor 1-alpha (HIF-1), yet inadequate vascular response leads to cellular necrosis (Kerachian et al., 2009).
- Osteocyte apoptosis: Dysregulated pathways involving caspase activation accelerate trabecular bone death.
- Matrix degradation: Upregulation of MMP-9 and MMP-13 destabilises the extracellular matrix, accelerating collapse.

Regenerative Mechanisms Of BM-MNCs

BM-MNCs represent a heterogeneous population containing mesenchymal stem cells, haematopoietic progenitors, and endothelial precursors (Zhao et al., 2012). Their therapeutic efficacy arises from multiple mechanisms:
1. Osteogenic differentiation: Mesenchymal precursors differentiate into osteoblasts under the regulation of transcription factors such as RUNX2 and osterix (Gangji et al., 2011).
2. Angiogenic stimulation: Endothelial progenitors secrete vascular endothelial growth factor (VEGF), promoting neovascularisation within necrotic bone.
3. Paracrine signalling: Cytokines including interleukin-6 and stromal-derived factor-1 modulate local inflammation and recruit host reparative cells.
4. Immunomodulation: BM-MNCs suppress pro-apoptotic cytokines, thereby prolonging osteocyte viability.

Clinical Translation

Hernigou et al. (2002) demonstrated the clinical benefits of autologous BM-MNC implantation during core decompression, reporting delayed progression and reduced collapse rates. Subsequent studies confirmed improvements in pain, function, and MRI-detected bone healing (Zhao et al., 2012; Gangji et al., 2011).

The procedure typically involves aspirating bone marrow from the iliac crest and retrieving only the monocytes which are a part of the mononuclear fraction and adventitious reticular cells which can be called as multipotent stromal cells known as mesenchymal stem/Stromal cells , and injecting them into the necrotic lesion under fluoroscopic control. Care should be taken to avoid neutrophil and Lymphocyte contamination.The monocytes under the influence of Granulocyte colony stimulating factor injections (Subcutaneous administration) or alpha granules of Platelet rich plasma gets converted into stemcells invivo and the adventitious reticular cells cannot become hematopoietic stemcells but they can differentiate into Mesenchymal lineages such as osteoblasts;chondrocytes and adipocytes .The Adventitious Reticular cells are Mesenchymal stromal cells in bone marrow that support hematopoiesis and can differentiate into various Mesenchymal cell types but they donot naturally convert into hematopoietic stemcells.(Bianco P etal .;2000;Bianco P etal.;2008;Caplon A.I.;2010) This relatively low-morbidity intervention has become a cornerstone of biological management of early AVN (Daltro et al., 2018).

Ethical And Regulatory Considerations

Clinical application of BM-MNCs mandates strict ethical oversight. Research protocols require approval from Institutional Ethics Committees and adherence to Good Clinical Practice (GCP) standards. Moreover, translational work in regenerative medicine exemplifies the indispensable role of doctoral scientists, whose training under UGC's 2009 and 2018 regulations ensures methodological rigour and accountability.

Future Directions

Emerging research also highlights the role of genetic profiling and personalised medicine in predicting therapeutic outcomes. Biomarkers such as VEGF expression levels, RUNX2 polymorphisms, and circulating exosomes may serve as predictive indicators for the success of BM-MNC therapy (Zhao et al., 2012; Gangji et al., 2011). Integration of artificial intelligence (AI)-based image analysis and 3D bioprinting of scaffolds are additional avenues being explored to optimise bone regeneration (Mao and Mooney, 2015; OECD, 2015). These innovations require interdisciplinary collaborations led by trained scientists with doctoral expertise.

Despite encouraging outcomes, variability in cell yield, patient selection, and long-term durability of results remains a challenge. Integration of BM-MNCs with biomaterial scaffolds, platelet-rich plasma, and gene-enhancement techniques may further augment efficacy (Mao and Mooney, 2015). Continued leadership from Ph.D./D.Sc. scientists will be essential in navigating these frontiers.

CONCLUSION

BM-MNC therapy represents a paradigm shift in the management of early-stage AVN, offering biological repair rather than symptomatic palliation. Genetic insights and molecular advances have elucidated the regenerative potential of these cells. This field epitomises the interface between basic science and clinical orthopaedics, underscoring the pivotal role of Ph.D./D.Sc. scientists working under UGC standards in advancing regenerative medicine.

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REFERENCES

1. Assouline-Dayan, Y., Chang, C., Greenspan, A., Shoenfeld, Y. and Gershwin,

M.E., 2002. Pathogenesis and natural history of osteonecrosis. Seminars in Arthritis and Rheumatism, 32(2), pp.94–124.
2. Daltro, G., Fortuna, V., Almeida, B., Souza, E., Duarte, M., and Reis, A., 2018. Cell therapy in avascular necrosis of the femoral head: a systematic review of the literature. Stem Cell Research & Therapy, 9, p.1–12.
3. Gangji, V., De Maertelaer, V. and Hauzeur, J.P., 2011. Autologous bone marrow cell implantation in the treatment of non-traumatic osteonecrosis: five-year follow-up of a prospective study. Bone, 49(5), pp.1005–1009.
4. Hernigou, P., Beaujean, F. and Lambotte, J.C., 2002. Cell therapy of hip osteonecrosis with autologous bone marrow grafting. Clinical Orthopaedics and Related Research, 405, pp.14–23.
5. Jones, L.C., 2015. Pathophysiology of osteonecrosis. Instructional Course Lectures, 64, pp.27–36.
6. Kerachian, M.A., Séguin, C. and Harvey, E.J., 2009. Glucocorticoids in osteonecrosis of the femoral head: a new understanding of the mechanisms. Journal of Steroid Biochemistry and Molecular Biology, 114(3–5), pp.121–128.
7. Mao, A.S. and Mooney, D.J., 2015. Regenerative medicine: Current therapies and future directions. Proceedings of the National Academy of Sciences, 112(47), pp.14452–14459.
8. Mont, M.A. and Hungerford, D.S., 2006. Non-traumatic avascular necrosis of the femoral head. Journal of Bone and Joint Surgery, 88(5), pp.1117–1132.
9. Moya-Angeler, J., Gianakos, A.L., Villa, J.C., Ni, A. and Lane, J.M., 2015. Current concepts on osteonecrosis of the femoral head. World Journal of Orthopedics, 6(8), pp.590–601.
10. UGC, 2009. Minimum Standards and Procedure for the Award of M.Phil./Ph.D. Degree Regulations. New Delhi: University Grants Commission.
11. UGC, 2018. University Grants Commission (Minimum Standards and Procedure for Award of Ph.D. Degree) Regulations. New Delhi: University Grants Commission.
12. Zhao, D., Cui, D., Wang, B., Tian, F., Guo, L., Yang, L., Liu, B. and Yu, X., 2012. Treatment of early stage osteonecrosis of the femoral head with autologous bone marrow stem cells combined with core decompression. Chinese Medical Journal, 125(15), pp.2610–2616.