Orthobiologics: Scientific background

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Tissue engineering is a term popularised in the 1990s and familiar to orthopaedic surgeons, developed on a paradigm of interplay between cells, materials, and molecules. The paradigm is a useful way to consider regenerative medicine, as it is thought that many future therapeutics will be developed from combinations of the three areas e.g. a scaffold impregnated with specific molecules can be seeded with cells. The term orthobiologics can be considered in this context, with a definition based around 'ortho', meaning an application in musculoskeletal tissue, and 'biologic' which is typically used to mean a naturally occurring substance with the ability to heal. However, the term should not be confused with a 'biologic medicine' or disease modification therapy.

Cells

Embryonic and induced pluripotent stem cells

In the natural world, the extraordinary capability of a stem cell to form nearly all cells in the developing human (pluripotency) coupled with the ability to self-renew is clear and can be illustrated with two examples: Embryonic Stem Cells (ESCs) and Induced Pluripotent Stem Cells (iPSCs). The former are found in the inner cell mass of the blastocyst and are key to development (Figure 1); the latter are somatic cells that in the laboratory have been reprogrammed back into a pluripotent state[1,2]. The biological capability of stem cells has huge therapeutic and regenerative potential, but in relation to orthopaedics ESCs and IPSCs are currently not close to use in patients in the clinic.

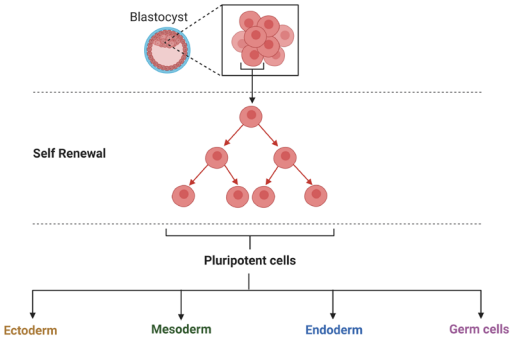

Figure 1: Schematic showing embryonic stem cells with characteristics of self-renewal and pluripotency. *Adapted from 'Human Embryonic Stem Cell Differentiation', by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates.*

Mesenchymal stem and stromal cells

Early studies on cells isolated from bone marrow identified a population of cells with the ability to differentiate into multiple cell types relating to musculoskeletal tissues; hence, the terminology 'mesenchymal stem cells' or 'MSCs' was proposed[3]. Following the identification of similar cell populations in other connective tissues e.g. fat, the International Society for Cellular Therapy (ISCT) proposed changing the name to 'mesenchymal stromal cells' (multipotent connective tissue cells of any organ), while retaining the acronym MSC, recognising that these populations rarely met defining criteria of true 'stem' cells. Their pro-regenerative effects after administration in vivo likely arise through the release of mediators, for example immunomodulatory, rather than engraftment and differentiation (Figure 2). In the remainder of this article the abbreviation MSC refers to Mesenchymal Stromal Cell. The ISCT also introduced minimum defining criteria that related to MSC characteristics; these criteria include cell adherence to plastic in culture, the presence or absence of certain cell surface markers, and the in vitro capacity to differentiate into osteoblasts, chondrocytes, and adipocytes[4]. More recently, the ISCT published a position statement on nomenclature[5], which suggests the tissue of origin should also be provided e.g. bone marrow, adipose, synovium or umbilical cord, and that "Unless there is rigorous functional evidence in vitro and in vivo to demonstrate the self-renewal and differentiation properties, the term mesenchymal stem cells should not be used."

Cell nomenclature and its importance

Understanding the behaviour of a cell and then accurately describing the cell to reflect this behaviour is key to avoid confusion, and this also applies to stem cells. The self-renewal ability and pluri- or multi-potency of ESCs, iPSCs or some adult stem cell populations such as haematopoietic stem cells are not generally attributable to cultured mesenchymal stromal cell populations. Attention has been drawn to the potential for confusion over the term 'stem cell therapy' when applied to MSCs, and the term 'stem cell' in the setting of orthobiologics is now discouraged[6,7]. Improved descriptions have now been proposed in relation to D—Donor, O—Origin tissue, S—Separation Method, E—Exhibited Characteristics (including potency), S—Site of Delivery, which can be abbreviated to DOSES[8].

Cell therapy

In addition to inconsistent nomenclature, heterogeneity in cell preparation (e.g. cell number, identity, purity) and manufacture (e.g. cultured or not) makes research evaluating the effectiveness of these products difficult, and the comparison across studies is at times impossible[9]. Systematic reviews have reported a high risk of bias within previous studies[10].

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MSCs can be broadly categorised on how they are extracted, processed, or manufactured. In general, we can consider two broad categories. In the first, autologous tissue is harvested, prepared, and delivered within the same visit ('point of care'). Such preparations have generally undergone relatively limited processing (minimally manipulated) and include concentrate of bone marrow aspirate, commonly abbreviated to BMAC, stromal vascular fraction (SVF) and microfragmented adipose tissue (MFAT). The preparations are heterogenous, with MSCs making up only a small fraction of the total cell content. In addition, what is delivered to individual patients is rarely characterised. This group of preparations are widely available as orthobiologic cell treatments in the UK, largely because of their relatively low cost and ease of delivery[11].

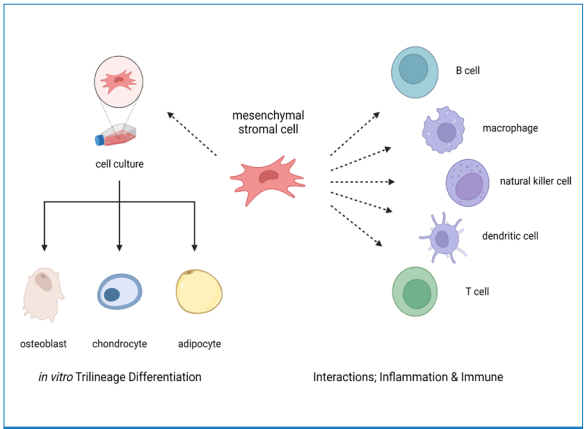

Figure 2: Mesenchymal stromal cell characteristics including in vitro tri-lineage differentiation and immunomodulation. *Created with BioRender.com.*

The second broad category is culture expanded cells. This features a period of manufacture in specialist GMP laboratories, where cells are cultured and expanded in number, which for autologous products, requires two patient interventions, the first for harvest and the second for delivery. Cells grown in a GMP facility can benefit from characterisation using markers on the cell surface and by assessment of their functional behaviour e.g., trilineage differentiation. This information can then be used to precisely quantify what is delivered to the patient, ensuring quality and safety before release to the clinic.

Autologous blood products

Products derived from autologous whole blood are attractive due to the presence of cells and factors with pro-regenerative activity, the ease of access, public acceptance, and the low morbidity of venepuncture. Products currently available include a spectrum of Platelet-Rich Plasma (PRP) and autologous anti-inflammatory preparations (AAIs).

The term PRP refers to an autologous blood preparation with a platelet concentration that is higher than baseline and is achieved through differential centrifugation with collection of the PRP from above the white blood cell layer. Platelets are known to release growth factors and cytokines that are able to induce pro-regenerative attributes in laboratory studies, including promoting proliferation and recruitment of cells, modulation of inflammatory responses, and stimulation of new blood vessel formation[12]. PRP represents a broad spectrum of preparations containing platelets, leukocytes, red cells, and over 300 different growth factors and cytokines[13]. Furthermore, the bioavailability of growth factors delivered depends on individual patient characteristics including comorbidities, platelet concentration, levels of leukocytes and red cells, and among other variables the method of activation[14]. PRP preparations are generally safe[15]. With increasing appreciation that many of the anti-inflammatory factors within blood arise from leukocytes rather than platelets, strategies focussing on concentrating leukocytes or the anti-inflammatory factors they release have been developed. These include autologous anti-inflammatory (AAI) preparations and platelet poor plasma (PPP).

Regenerative therapies and orthobiologics, represent an exciting field with many potential therapeutic options available to the surgeon. In common with other new treatments, it is important to consider not just the class of therapy but also how it works in relation to the target condition, who should receive the treatment, how it is manufactured and administered, and how effective and financially viable it is. Recent advances in science enhance our understanding of disease pathogenesis, mechanism of action of treatments, and patient stratification tools, which together with our ability to conduct clinical trials, will facilitate the acquisition of clinical evidence and subsequent impact. ■

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Selected references

- Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell.* 2006;126(4):663-76.
- Viswanathan S, Shi Y, Galipeau J, *et al.* Mesenchymal stem versus stromal cells: International Society for Cell & Gene Therapy (ISCT®) Mesenchymal Stromal Cell committee position statement on nomenclature. *Cytotherapy.* 2019;21(10):1019-24.
- Caplan AI. Mesenchymal Stem Cells: Time to Change the Name! *Stem Cells Transl Med.* 2017;6(6):1445-51.
- Murray IR, Chahla J, Safran MR, *et al.* International Expert Consensus on a Cell Therapy Communication Tool: DOSES. *J Bone Joint Surg Am.* 2019;101(10):904-11.
- Mussano F, Genova T, Munaron L, *et al.* Cytokine, chemokine, and growth factor profile of platelet-rich plasma. *Platelets.* 2016:27(5):467-71.

References

References can be found online at www.boa.ac.uk/publications/JTO.