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Embryonic stem cells: Understanding their history, cell biology and signalling ☆

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Abstract

Embryonic Stem cells offer enormous potential as a source of a variety of differentiated cells for cell therapy, drug discovery and toxicology screening. With the creation of human embryonic stem cell lines we now have a resource with the potential to differentiate into every tissue of the body. To fully harness this resource it is necessary to understand their biology. Here we give a background to their history, describe interesting elements of their cell biology and introduce the underlying signalling mechanisms that control their ability to self-renew and differentiate.

Keywords: Embryonic; Stem cell; History; Biology; Signalling; Review; Drug discovery; Toxicology; Cell therapy

Contents

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1. Introducing stem cells

Embryonic stem cells are now at the forefront of drug discovery facilitated by high throughput screening protocols, and are a much anticipated source for cell-based therapy to treat injuries and degenerative diseases. The selection of high-quality input material is essential and requires an exquisite understanding of basic stem cell biology. Research into this fascinating area is advancing rapidly, and although many aspects remain unravelled, we here aim to review the history and recent developments in this area. Firstly it is important to discuss the often confused terminology, beginning with the term 'stem cell' itself. At least two properties are generally considered to define a stem cell. Firstly, having an unlimited capacity for self-renewal without senescence, and secondly, the ability to terminally differentiate into one or more cell types in vivo and in vitro. This remarkable dual ability is clearly distinct from 'progenitor' or 'precursor' cells, which are derived from stem cells, but crucially lack the capacity to self-renew. These therefore represent cells which are intermediates to the production of mature cells, its sole progeny. The capacity of stem and progenitor cells to form differentiated offspring is described in terms of their differentiation potential or plasticity. Arbitrarily, 'pluripotent' cells are those cells whose fate has been determined by their relative position in the early blastocyst and are destined for either the inner cell mass (ICM) or the trophectoderm lineage. Indeed, pluripotent cells derived ex vivo from the early mouse embryo include both the embryonic stem (ES) and trophoblast stem (TS) cells, whose differentiated progeny exclusively represents that of the ICM (epiblast plus extra-embryonic primitive endoderm) or trophoblast lineage in vivo, respectively. Whereas mouse ES cells are able to differentiate into derivatives of all three embryonic germ layers, both in an in vivo and in vitro environment, human stem cells can be directed to differentiate in a trophoblast lineage as well. It has yet to be discovered if this feat is stem cell line-specific and it may be restricted to a limited subset of human ES cells or subject to ES cell derivation and subsequent cell culture methods. Cells derived from the gonadal ridges of aborted fetuses are pluripotent, too. These include the embryonic germ (EG) and the embryonic carcinoma (EC) cells; the latter isolated from spontaneously arising teratocarcinomas and are therefore karyotypically abnormal. Pluripotent cells are only surpassed in their developmental capacity by the truly 'toti-' or 'omnipotent' blastomeres from the early morula. However, blastomeres have not been shown to proliferate indefinitely and are therefore not classified as stem cells. 'Multipotent' adult or somatic stem cells are cells that are capable of self-renewal and can form multiple differentiated cell types, but all within a distinct tissue, organ or physiological system. They reside in a wide variety of tissues in the adult mammalian body and can attribute to the replenishing of mature cells and the extensive regeneration of damaged and diseased tissue. For instance, differentiated offspring of haematopoietic stem cells are oligopotent progenitors that in turn are able to further differentiate into every mature lineage of blood cells. The efficacy of this characteristic for cell-based therapies has now been demonstrated for some time in a large number of successful bone-marrow transplantations. Other multipotent stem cells are mesenchymal stem cells, which can differentiate into bone, cartilage and fat. The tissue-specific multipotent nature of these adult stem cells has been under much scrutiny the past years. It has been observed that, at least in vitro, multipotent adult stem cells can 'acquire' a differentiation pattern resembling a state of (pseudo-) pluripotency. This can happen either by fusion with other cell types resulting in mosaic karyotypes or, perhaps to a lesser extent, through a trans-differentiation process. Whatever mechanism might be responsible for this phenomenon, frequencies are low and it is not clear if either is a normal repair process in vivo and if large numbers of trans-differentiated cells can be obtained in vitro.