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Stem Cell Therapies to Recover Salivary Gland Function in Head and Neck Cancer Radiotherapy Patients

Introduction

In 2012 in the UK alone, 11,152 new cases of head and neck cancers were diagnosed[(1)]. Standard treatment options, as with many cancers, are surgery, chemotherapy and radiotherapy or commonly a combination of two or more of these[2]. The dose the patient is exposed to in a course of radiotherapy is multitudes higher than the effective dose received by a patient to produce a, for example, bitewing or periapical radiograph commonly used in dentistry (2,000 mSv/fraction[(2)] vs. 0.0003-0.022mSv[(3)] respectively). Radiotherapy of this high a dose results in co-irradiation of surrounding soft tissues with a common side effect of ablation or severe reduction of salivary gland function. This results in 'dry mouth syndrome' or xerostomia and can have a severe impact on the quality of life of the patient post-irradiation, affecting their ability to speak, masticate, swallow[(4)] and not to mention the role saliva has in maintaining healthy oral tissues[(5)].

Salivary Glands

Salivary glands are made of a series of ducts; acini of secretory cells found at the terminus of the gland produce saliva, which drains into intercalated ducts, which in turn drains in to the excretory duct[(6)]. Recent work has suggested that in a healthy salivary gland, maintenance and replacement of ageing or injured cells works similarly to the pancreas or liver, i.e. self-renewal of fully differentiated cells instead of relying on a population of tissue stem cells[(6)]. The most common view as to why salivary gland function is lost on irradiation is due to a bifaceted loss of function. Secretory acinar cells are damaged from the radiotherapy causing either apoptosis or membrane damage-related dysfunction resulting in early loss (days 1 to 60 post-irradiation) of saliva production[(5)]. The radiation also effectively sterilises many, if not all, salivary gland stem/progenitor cells (SSPCs) located in the excretory and intercalated ducts. Because of this, once the acinar cells senesce or undergo apoptosis, the lack of SSPCs to replace these acinar cells results in sustained hyposalivation (days 60 – 240 post-irradiation)[(5)].

Stem Cells

Differentiation is the process by which stem cells lose their omnipotence to form any cell type in the body through to progenitor cells of certain tissues[(7a)] (such as haematopoietic stem cells (HSCs), found in bone marrow that can give rise to any form of blood cell[(7b)]), and finally to post-mitotic, specialised cell-types. Human Embryonic Stem Cells (hESCs) have been investigated in the past 20 years for use in therapeutic procedures due to their abilities to form any cell type in the body and to self-renew indefinitely. However, there are some drawbacks to using hESCs, especially concerning the ethical issues surrounding the source[(8)]. Furthermore, hESCs have been shown to be highly teratogenic *in vitro*, a trait they share with induced pluripotent stem cells (iPSCs) (hESCs induced to begin differentiation when exposed to certain conditions, thus slightly reducing the range of cell-types they can become)[(8, 9)], reducing their viability as a candidate for therapy. Adult Stem Cells (ASCs) is the term used to describe tissue specific stem cells in adults, and are used in repair and maintenance of tissues, without any of the ethical concerns associated with hESCs. ASCs also have the added bonus of minimising immune rejection if transplanted as they can be harvested from the patient's own body, however this harvesting an isolation is difficult to achieve[(8)]. Promising new candidates for stem cell therapy are Mesenchymal Stem Cells (MSCs), adult multipotent progenitors that can be of bone marrow, adipose tissue (and many other) origin with the capacity to

differentiate into many cell types, as they can self-renew, expand rapidly and can be easily collected[10].

Therapies

One premise of stem cell therapies to rescue salivary gland function involves harvesting viable stem cells from the patient, co-culturing them *in vitro* with patient acinar cells causing transdifferentation of the stem cells, and transplantation post-irradiation[10, 11]. Transdifferentiation is the process by which pluri-/multipotent stem cells can switch cellular phenotype via the processes of dedifferentiation and redifferentiation into another cell lineage[11]. MSCs from adipose[11] and bone marrow[10] have both been successfully transdifferentiated, via a co-culture method with acinar cells to produce α-amylase-secreting cells, the exact mechanism of which is yet to be determined, however.

It is also worth mentioning that the above therapies are based on the condition of full ablation of salivary gland function and therefore in need of an external source of stem cells for regeneration. Partial ablation could potentially mean a population of viable of SSPCs still present. This population of SSPCs can be harvested and cultured *in vitro* with various growth factors, increase in size (and form 'salispheres') over time with promising work involving salisphere transplantation back into mouse models resulting in 70% recovery of SG function[5]. Early data has even shown human SSPC salispheres to show some differentiation into structures containing acinar and ductal-like structures[5].

Conclusion

The use of stem cells as an avenue for therapeutic approaches still requires a lot of investigation and a lot of challenges yet to overcome, however induced transdifferentiation of mesenchymal stem cells provides an interesting breakthrough. Further work in this field could help remove xerostomia as a consequence of radiotherapy, or eventually be applied to other causes of xerostomia, and drastically improve the quality of life for thousands.

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