Regenerative Endodontics: Burning Questions

Anthony J. Smith, PhD, and Paul R. Cooper, PhD

Abstract

Pulp regeneration and its clinical translation into regenerative endodontic procedures are receiving increasing research attention, leading to significant growth of the published scientific and clinical literature within these areas. Development of research strategies, which consider patient-, clinician-, and scientist-based outcomes, will allow greater focus on key research questions driving more rapid clinical translation. Three key areas of focus for these research questions should include cells, signaling, and infection/inflammation. A translational pathway is envisaged in which clinical approaches are increasingly refined to provide regenerative endodontic protocols that are based on a robust understanding of the physiological processes and events responsible for the normal secretion, structure, and biological behavior of pulpal tissue. *(J Endod 2017;43:S1–S6)*

Key Words

Cell signaling, clinical translation, dentin, inflammation, pulp, regeneration, regenerative endodontics, stem cells

Significance

This article explores key priorities and strategic areas of focus for clinical translation of regenerative endodontics. It provides a translational pathway robustly underpinned by sound scientific principles with a strong focus on development of effective clinical protocols.

Dentistry has long been a pioneer of regenerative medicine by using many biologically inspired therapeutic approaches (1). Although the term *regenerative endodontics* has become specifically associated with revascularization procedures originally proposed more than 50 years ago (2), the wealth of research activity in the area of dental pulp regeneration emphasizes the range of opportunities to clinically translate the many exciting advances in pulp biology for a wide variety of new therapies. Rapid progress toward such clinical translation demands focus and prioritization of key questions within the research agenda, and this article seeks to elucidate a number of these.

A Web of Science search for the period 1973–2016 by using the term "dental pulp regeneration" identifies 1064 publications, only approximately 4% of which were published before 2000 (Fig. 1). Clearly, absolute numbers will vary with the specific words used in the search term (eg, repair versus regeneration, etc), and some publications will be missed through inappropriate choice of key words by authors, but nevertheless, there has been a considerable increase in apparent activity in this area during the last decade. This significant proliferation of the newer published literature can obscure some of the existing literature in the field, and many key publications are often not readily visible or being cited. Basing future research questions and agenda on robust appraisal and interpretation of the existing published literature will help to avoid "reinventing the wheel," refine our research focus, and more rapidly advance the field. Nevertheless, that focus may be deflected by the desired outcomes for regenerative endodontics, and consideration of the context of these outcomes (Fig. 2) may be valuable (3). Initial prioritization of those patient-centered outcomes at the base of the pyramid that is followed by the clinician-related outcomes and rising to the scientist-centered outcomes at the peak of the pyramid offers a valuable approach to identification of an effective path leading to clinical translation. This in no way detracts from the need to still understand and address scientist- and clinician-centered factors to provide optimal therapeutic solutions for patient-centered outcomes, but it helps to focus attention on the extent to which each factor needs to be fully resolved at each step along the clinical translation pathway.

For clarity of presentation, this article will consider 3 key areas of focus: cells, signaling of regenerative events, and infection/inflammation.

Cells

Must Newly Regenerated Cells Behave like Odontoblasts?

The concept of tissue regeneration implies generation and secretion of new tissue by cellular activity. Although the formative cells of soft connective tissues like pulp share the fibroblast phenotype, dentin is secreted by the highly specialized odontoblasts,

From the School of Dentistry, University of Birmingham, Birmingham, United Kingdom.

Address requests for reprints to Dr Anthony J. Smith, School of Dentistry, University of Birmingham, 5 Mill Pool, Edgbaston, Birmingham B5 7EG, United Kingdom. E-mail address: a.j.smith@bham.ac.uk

0099-2399/$ - see front matter

http://dx.doi.org/10.1016/j.joen.2017.06.002

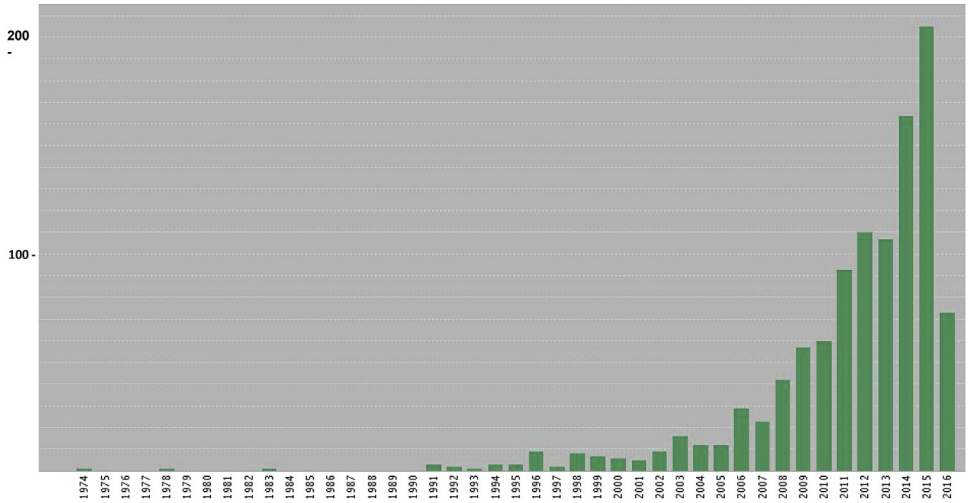

Figure 1. Chart of numbers of publications in each year derived from search of the Web of Science by using the search term "pulp regeneration".

which are responsible for the tubular and mineralized structure of this tissue. The mineralized nature of dentin is important for its structural role as a component of the tooth, but the necessity for its tubular morphology in a regenerated tissue could be questioned. In an endodontic therapeutic situation, any mineralized tissue seal (tubular or atubular) for the pulp may suffice, and an atubular dentin matrix offers reduced permeability and possibly a more effective seal to protect the pulp. However, it has become apparent that the roles of true odontoblasts are not simply matrigenic (secretory) alone, and a number of other complex functions for these cells are starting to be characterized including local communication, environmental sensing, and innate immunity and mediation of pain transmission (4, 5). These diverse but linked functions, and others that may yet be identified, highlight the specialized nature of the odontoblast, and a long-term goal should be to develop regenerative endodontic approaches that fully exploit the functional and behavioral ranges of these cells. In the shorter term, however, regenerative procedures that are based on cells secreting any type (tubular or atubular) of mineralized matrix may suffice and illustrate how consideration of patient-centered versus clinician-centered versus scientist-centered outcomes (Fig. 2) can be helpful.

How Can We Effectively Deliver Stem/Progenitor Cells for Regenerative Endodontics?

There is considerable merit in learning from advances in other areas of regenerative medicine where various cell transplantation therapies have been introduced. Isolation of pulp stem cells to good manufacturing practices standards for medical uses (6) represents an important step toward development of tissue engineering–based regenerative endodontic therapies, but without specialist hospital

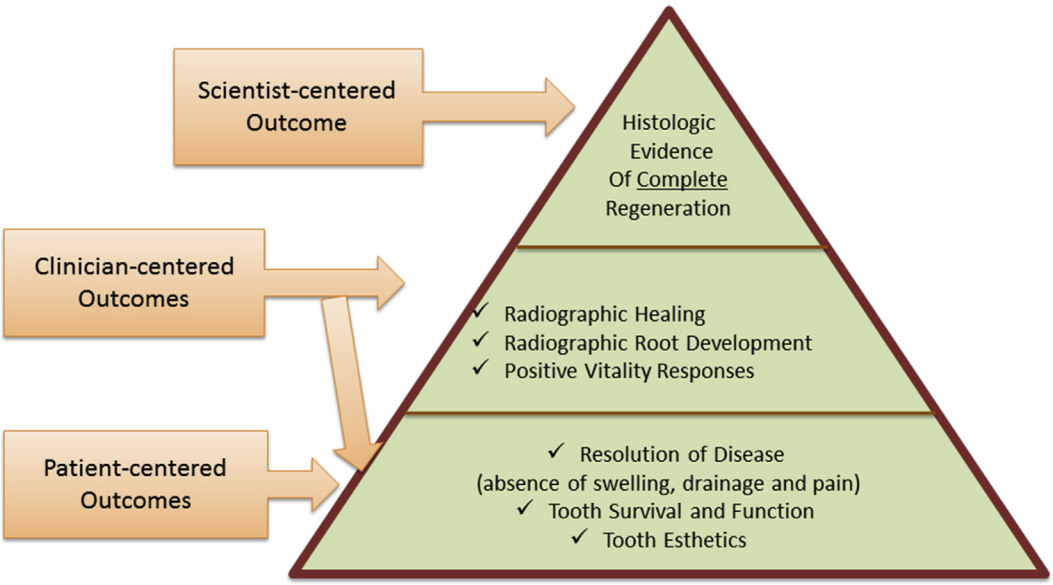

Figure 2. Schematic representation of hierarchy of patient-, clinician-, and scientist-centered outcome visions. Reproduced from Diogenes AR, Smith AJ. Regenerative endodontics. In: Rotstein I, Ingle JI, eds. Ingles Endodontics. 7th ed. Shelton, CT: People's Medical Publishing House–USA; 2016.