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ORIGINAL ARTICLE

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Osteoinduction, osteoconduction and osseointegration

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Abstract Osteoinduction is the process by which osteogenesis is induced. It is a phenomenon regularly seen in any type of bone healing process. Osteoinduction implies the recruitment of immature cells and the stimulation of these cells to develop into preosteoblasts. In a bone healing situation such as a fracture, the majority of bone healing is dependent on osteoinduction. Osteoconduction means that bone grows on a surface. This phenomenon is regularly seen in the case of bone implants. Implant materials of low biocompatibility such as copper, silver and bone cement shows little or no osteoconduction. Osseointegration is the stable anchorage of an implant achieved by direct bone-to-implant contact. In craniofacial implantology, this mode of anchorage is the only one for which high success rates have been reported. Osseointegration is possible in other parts of the body, but its importance for the anchorage of major arthroplasties is under debate. Ingrowth of bone in a porous-coated prosthesis may or may not represent osseointegration.

Keywords Osteoinduction · Osteoconduction · Osseointegration

Introduction

The terms osteoinduction, osteoconduction and osseointegration are frequently, but not always correctly, used terms in many orthopaedic papers. To give but one example of incorrect terminology, arthroplasties are commonly claimed to be osseointegrated based only on radiographic evidence, despite the fact that the resolution of radiography alone is too poor to determine whether an implant is osseointegrated or not. The aim of this paper is to first briefly explain and define these terms and then to look at them in some detail. Osteoinduction, osteoconduction and osseointegration are now the subject of much discussion, e.g. in connection with bone morphogenic proteins (BMP), bone growth factors and direct bone anchorage, respectively. Suggested definitions of the terms osteoinduction, osteoconduction and osseointegration read as follows:

Osteoinduction. This term means that primitive, undifferentiated and pluripotent cells are somehow stimulated to develop into the bone-forming cell lineage. One proposed definition is the process by which osteogenesis is induced [43].

Osteoconduction. This term means that bone grows on a surface. An osteoconductive surface is one that permits bone growth on its surface or down into pores, channels or pipes. Wilson-Hench [43] has suggested that osteoconduction is the process by which bone is directed so as to conform to a material's surface. However, Glantz [18] has pointed out that this way of looking at bone conduction is somewhat restricted, since the original definition bears little or no relation to biomaterials.

Osseointegration. This was first described by Brånemark and co-workers [12]. The term was first defined in a paper by Albrektsson et al. [4] as direct contact (at the light mi-

croscope level) between living bone and implant. Osseointegration is also histologically defined in *Dorland's Illustrated Medical Dictionary* as the direct anchorage of an implant by the formation of bony tissue around the implant without the growth of fibrous tissue at the bone–implant interface. Since the histological definitions have some shortcomings, mainly that they have a limited clinical application, another more biomechanically oriented definition of osseointegration has been suggested: "A process whereby clinically asymptomatic rigid fixation of alloplastic materials is achieved, and maintained, in bone during functional loading" [46]. The rigid fixation of an implant in orthopaedic praxis can be determined using radio-stereophotogrammetic (RSA) techniques and, at least in craniofacial implantology, resonance frequency analysis (RFA) [28].

Osteoinduction and its importance for bone healing

In addition to the differentiated bone cells, i.e. osteoblasts, osteoclasts and osteocytes, bone and adjacent tissues contain a number of less differentiated cells. These undifferentiated cells are of utmost importance for proper bone healing or anchorage of an implant, since they can be recruited to form osteoprogenitor cells [45] and, with time, develop into differentiated bone cells (Fig. 1). With the correct stimulus (the inductive agent), an undifferentiated mesenchymal cell can be transformed into a preosteoblast, a process which constitutes bone induction. The classical papers describing bone induction at various host sites were published a long time ago [20, 25, 40]. These authors used gall bladder epithelium, alcohol extracts of bone and transplants to muscles or the anterior chamber of the eye, respectively, to demonstrate heterotopic bone formation. The safest way to demonstrate whether a particular agent is osteoinductive or not is still to inject it into a heterotopic bed such as a muscle pouch and to analyse any potential bone formation (Fig. 2). Inductive agents naturally function in bone surroundings too, but it is difficult to differentiate between bone induction and bone conduction in an orthotopic site.

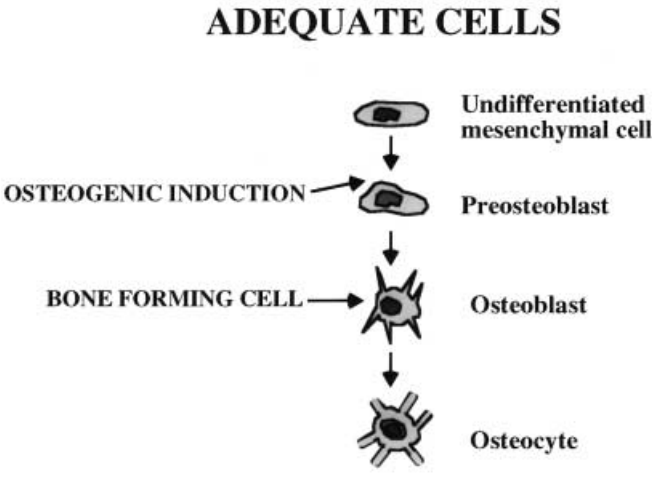

Fig. 1 At the time of injury, adequate cells for bone repair are both undifferentiated and differentiated bone cells. The majority of newly formed bone depends on the undifferentiated cells that are induced to become preosteoblasts

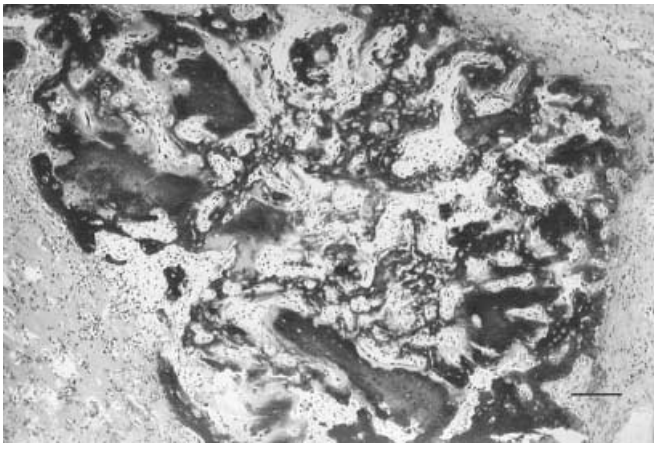

Fig. 2 The best way to demonstrate whether a specific agent is osteoinductive is to inject it into a soft tissue pouch, where bone formation does not occur under normal conditions. BMP-7 induced bone formation 19 days after injection into a subcutaneous site in a rat. Toluidine blue. *Bar*, 100 μm

More modern research into osteoinduction dates back to Urist's experiment in the mid-1960s [39]. Demineralised bone was used as an osteoinductive agent. Later, Urist et al. [41] isolated a soluble glycoprotein called BMP as the inductive agent. The BMP belong to the transforming growth factor (TGF)-β-family of growth factors. There are at least 15 different BMP [34], of which BMP-2 and BMP-7 seem to be particularly interesting. To date, a great number of research projects involving various types of BMP are being conducted (for reviews, see [24, 34]). BMP are naturally released in response to trauma or at bone remodelling and are the only known inducive agents [26]. However, physical stimuli such as stress or types of electrical signals otherwise applied have been regarded as, directly or indirectly, influencing bone induction [10, 13, 14, 44].

Osteoinduction, i.e. the recruitment of immature cells and the stimulation of these cells to develop into preosteoblasts, is a basic biological mechanism that occurs regularly, e.g. in fracture healing and implant incorporation. Even if pre-existing osteoblasts (i.e. before the injury) may help to form new bone, it is generally agreed that such pre-existing cells only contribute a minor portion of the new bone needed in a fracture-healing situation [16, 17]. According to Frost [16, 17] (Fig. 3), the inevitable bone, marrow and soft tissue injury triggers the subsequent repair by sensitising different types of surviving cells. Si-

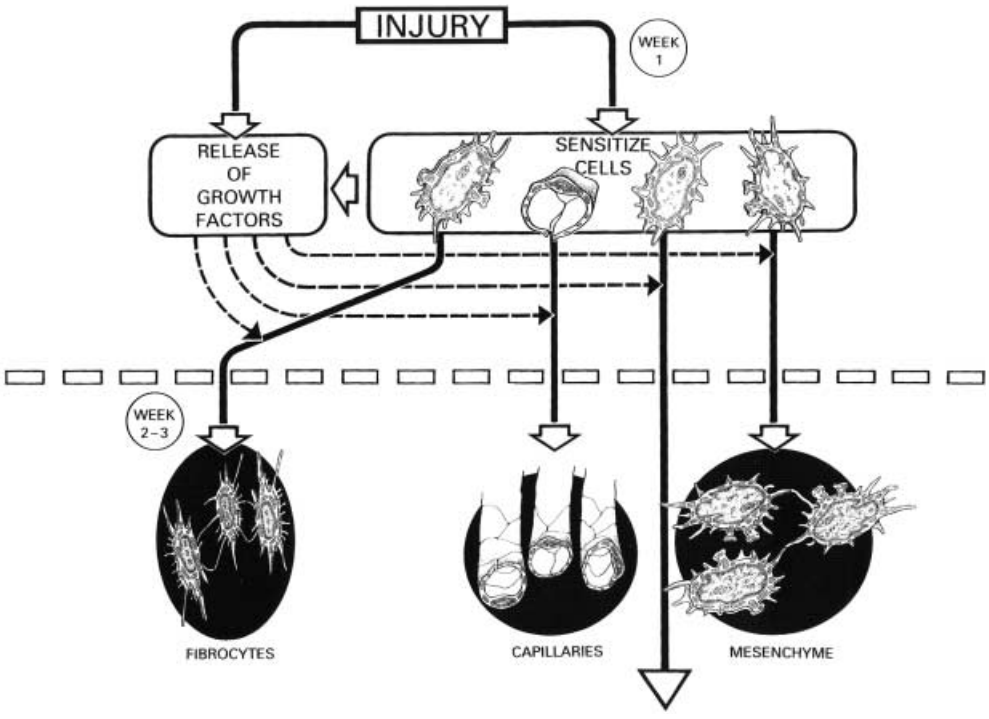

Fig. 3 According to Frost's theory, injury triggers off a healing response by the release of growth factors and sensitising of cells. This is a primitive healing response with stimulation of many different types of cells

multaneously, the injury releases local, biochemical and biophysical messengers that help cells to respond and that guide them to respond in the proper manner. Some of these messengers guide the differentiation and organisation of cells, while others provide mitogens. This initial part of the healing response thus includes osteoinduction, a process that starts immediately after the injury and is very active during the first week thereafter, even though the action of the newly recruited preosteoblasts is not obvious until several weeks later, in the callus stage.

Osteoconduction and its importance for bone healing

Bone growth on an implant surface depends on the action of differentiated bone cells. These cells may originate either in pre-existing preosteoblasts/osteoblasts that are activated by trauma or in cells recruited from primitive mesenchymal cells by osteoinduction [16, 17]. In the practical situation, therefore, osteoconduction (Fig. 4) depends to a fairly large extent on previous osteoinduction. The debate concerning whether or not a particular biomaterial acts as an osteoinductor may be slightly academic, since the injury at placement is sufficient to recruit previously undifferentiated bone cells.

Various types of bone growth factors are necessary for bone formation. Furthermore, bone growth, including bone conduction, does not occur without a proper blood supply. Albrektsson [1] studied bone conduction and remodelling in vivo and came to the conclusion that so-called full vascularisation was necessary for bone formation. It is there-

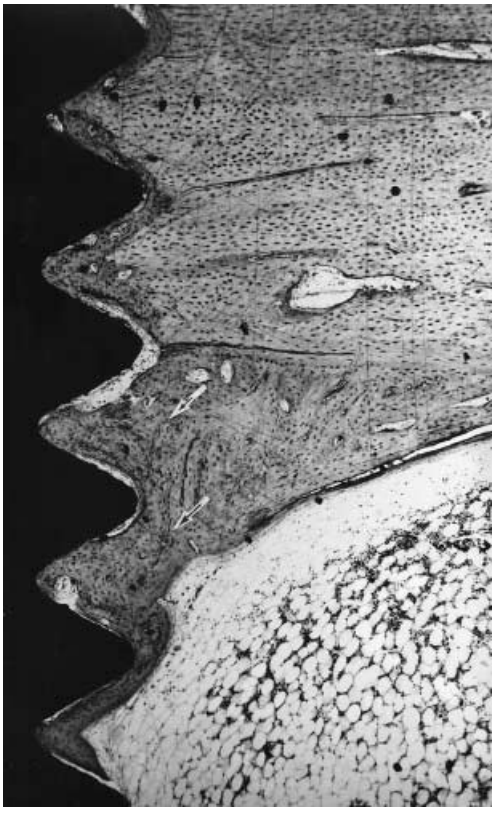

Fig. 4 In biomaterials science, osteoconduction means growth of bone on the surface of a foreign material, as seen in the lower part of this titanium screw implant (*arrows*). Distance between thread peaks, 600 μm

fore not surprising that the principal action of many growth factors is both mitogenic and angiogenic [37]. Growth factors that regulate bone tissue in one way or another include insulin-like growth factor (IGF I, II), fibroblast growth factor (FGF), TGF-β and platelet-derived growth factor (PDGF). The IGF are also called somatomedins. The growth factors are small proteins that serve as signalling agents for cells [37] (see the paper by Lind, this volume, for a more detailed discussion of various growth factors).

However, in the case of implants, bone conduction is not only dependent on conditions for bone repair, but also on the biomaterial used and its reactions. Bone conduction is not possible on certain materials such as copper and silver [3]. However, bone conduction is seen with biomaterials not regarded as ideal from the point of view of biocompatibility, such as stainless steel [22] and obviously materials of high biocompatibility such as commercially pure (c.p.) titanium. Bone conduction on implants may be quantified. There is a significant difference in the amount of bone that grows on seemingly similar materials such as c.p. titanium and titanium 6-aluminum 4-vanadium [23]. However, the clinical implications of this difference remain unknown.

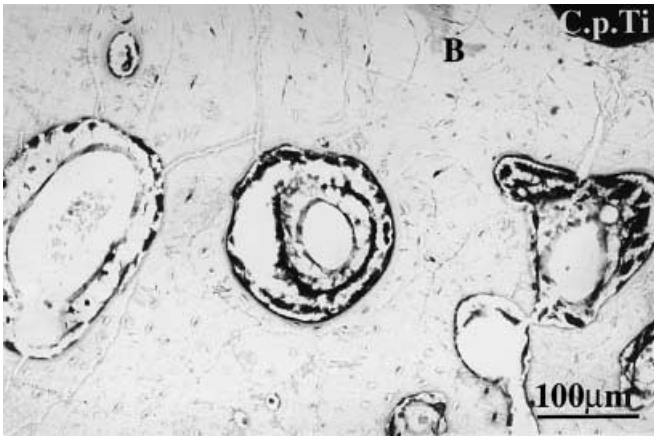

Fig. 5 Simultaneous bone formation and resorption at the interface between bone (*B*) and a commercially pure titanium (*c.p. Ti*) implant. There are three cavities arranged in a horizontal line in the middle of the figure. In the left cavity, red dominates, i.e. positive staining for acid phosphatase meaning active bone resorption. In the middle cavity, blue dominates, i.e. positive staining for alkaline phosphatase, meaning active bone formation. In the right cavity, there is red and blue staining, i.e. both bone formation and resorption. *Bar*, 100 μm

Osseointegration of implants

Brånemark, who introduced this term, suggested the spelling "osseointegration" instead of "osteointegration", and the original spelling is preferred in this paper. Osseointegration is not an isolated phenomenon, but instead depends on previous osteoinduction and osteoconduction. Thus materials that are too toxic to allow osteoconduction will not be osseointegrated either. However, many materials show at least some bone attachment, which has inspired bone pathologists to regard osseointegration as a simple foreign body reaction [15], whereas more clinically oriented scientists have rejected such a view. Osseointegrated implants have undergone a real breakthrough in oral and craniofacial implantology, yielding excellent functional results, in contrast to alternatively anchored implants, which have generally shown very poor success rates [6, 12, 35, 36]. Even if initial osseointegration is dependent on bone induction and conduction, the term implies that the bone anchorage is maintained over time. Cylindrical implant designs (without threads), rough plasma-sprayed surfaces and overloading represent factors that may lead to secondary failure of osseointegration [2, 4].

The ultrastructure of the bone–titanium interface in osseointegration demonstrates an amorphous layer from 20–40 to 500 nm thick. Some investigators [5] have described collagen and calcified tissue in this zone, whereas others [32] have failed to verify these findings. This zone is too narrow to be seen at the light microscope level of resolution. At the light microscope level, direct bone contact, osteogenesis and bone resorption occur simultaneously [31] (Fig. 5). From a purely biomechanical viewpoint, Skalak and Zhao [33] have demonstrated that when a hole slightly smaller than the implant diameter is prepared for implant placement, force-fitting stress increases installation torque and initial stability can be induced at a similar magnitude as seen with roughened implants.

Oral implants retrieved from patients despite remaining stability have shown that there does not seem to be 100% bone attachment. Implants retrieved after clinical function for up to 17 years showed an average of 70–80% bone contact with an absolute minimum of 60% [7]. Functioning osseointegrated implants demonstrate interfacial bone density similar to that of the bone in which the implant was implanted [38]. Even if long-term functioning osseointegrated implants show what seems to be similar bone tissue reactions, osseointegration might be able to be achieved more rapidly than otherwise observed. Such potentially accelerated osseointegration has been indicated by results from experiments with hydroxyapatite coating [19], using intermediary roughened implants [42], after hyperbaric oxygen treatment [30] or by using anodised c.p. titanium with artificially enhanced oxide layers [9]. Acceleration of osseointegration may depend on the removal of negative tissue conditions or optimisation of the biomaterial rather than on an actual increase in the rate of bone response.

Much less attention has been paid to the possibility of establishing osseointegration in orthopaedic surgery than in oral and craniofacial surgery. The original notion that polymerised bone cement may be histologically osseointegrated has not been confirmed in more recent investigations [29]. Histological sections to reveal true bone-to-im-

Fig. 6 Hydroxyapatite-coated vertebral screw in a goat. Osseointegration is evident. *Bar*, 1000 μm (Courtesy of Dr. B. Sandén, Uppsala University)

plant contact need to be quite thin (of the order of 10–20 μm) to really reveal osseointegration. Thicker sections have a shadow effect [21] that make it impossible to state whether or not true direct bone contact has been achieved. Apart from poor resolution, this is the reason why common radiographs are of little value in the diagnosis of osseointegration. The question is whether it is really possible to establish osseointegration of conventional orthopaedic arthroplasties with the combined use of less biocompatible materials, interfacial heat due to curing bone cement, drilling or reaming without a cooling agent and too rapid loading. It is known that interfacial implant movement of more than 150 μm will inevitably lead to soft tissue formation instead of bone, for instance [11]. Even if one- or two-point bone contact can be demonstrated, this need not represent actual osseointegration of the entire implant.

Screw-type implants inserted using a modified minimally traumatising technique have been convincingly osseointegrated, e.g. in hip arthroplasties [8] and interphalangeal implants [27] or vertebral screws (Fig. 6). However, whether or not osseointegration will become as important a type of anchorage in orthopaedics as in oral and craniofacial implantology will depend on the reported long-term clinical results of this type of anchorage.

Conclusion

Osteoinduction, osteoconduction and osseointegration are interrelated, but not identical phenomena. Osteoinduction is part of normal bone healing and is responsible for the majority of newly formed bone, e.g. after a fracture or the insertion of an implant. The implant itself may be osteoinductive, but this is not a prerequisite for bone induction. Osteoconduction is a term now usually used in conjunction with implants. Osteoconduction and osseointegration both depend not only on biological factors, but also on the response to a foreign material. The osteoconductive response may be rather short lived, but successful osseointegration maintains its bone anchorage over a long period.

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