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Biomaterials for the programming of cell growth in oral tissues: The possible role of APA

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Abstract:
Examples of programmed tissue response after the interaction of cells with biomaterials are a hot topic in current dental research. We propose here the use of anodic porous alumina (APA) for the programming of cell growth in oral tissues. In particular, APA may trigger cell growth by the controlled release of specific growth factors and/or ions. Moreover, APA may be used as a scaffold to promote generation of new tissue, due to the high interconnectivity of pores and the high surface roughness displayed by this material.

Keywords: APA; biomaterials; cell growth

Background:

Historically, the function of biomaterials has been to replace diseased or damaged tissues **[1]**. Whereas first generation biomaterials only aimed to match the physical properties of the replaced tissues with the lowest toxic response in the host (i.e. being 'bioinert'), second generation biomaterials, which include glasses, ceramics, glass-ceramics and composites, form a strong bond to bone and connective tissues **[1]**. Further advancements in material science and nanoengineering have led to third-generation 'bioactive' biomaterials. This means eliciting specific molecular interactions with cells, enhancing cell and/or extracellular matrix proliferation, cell differentiation and organization, and activating genes to stimulate these activities. Thus, tissue regeneration can be programmed by a well-characterized biomaterial-cell interaction **[1].**

Examples of programmed tissue response after the interaction with biomaterials are currently emerging in dental research, with a special focus on the osseointegration process **[2, 3]**. We propose here functionalized anodic porous alumina (APA) as a third generation biomaterial for the programming of cell growth in oral tissues.

Anodic porous alumina:

APA is a nanostructured material that can be prepared in macroscopically extended (i.e. cm^2 scale) surfaces [4]. APA is a rigid matrix of porous aluminum oxide (Al_2O_3), obtained by controlled anodization of a high purity (~99.999%) aluminum electrode in an acid electrolytic bath, after prior surface smoothing by electropolishing. The pore diameter is upper limited by the pore cell size, which is determined in a coarse way by the type of acid, and in a fine way by the applied potential during potentiostatic anodization. Typically, pores of ~20, ~40, and ~200 nm diameter can be obtained. The pore diameter can be increased and made closer to the whole cell size (2-3 times the pore diameter) in a subsequent etching step. The pore arrangement can also be made locally ordered in hexagonal lattice domains of 1-3 µm diameter, mainly by finding the proper anodization voltage.

APA is an inert, hard, refractory and chemically resistant material. It is biocompatible, is not destroyed when in contact with biological fluids and is not toxic. On the other hand APA is not biodegradable, meaning that after being inserted in living tissues it cannot be dissolved in situ over time.

Potential applications in biology and medicine:

Some possible applications of APA are summarized in **Table 1 (see Supplementary material)**. Free-standing APA membranes are used for the purification of water from pathogens **[5]**. APA has also been proposed as a scaffold for microarrays, a tool used to evaluate gene expression of different tissues **[6]**. All these applications can be enhanced if APA pore functionalization is further exploited. In fact, by filling APA with either a polymer solution or nanoparticles, a "negative" nanocomposite (with inorganic matrix surrounding polymer "filler" units) or a composite with inorganic rigid matrix can be obtained, respectively. These options pave the way to promising biological applications. One of the authors (MS) has currently two project proposals under evaluation for applications of the above concepts in the field of biosensors and bioelectrodes, respectively. Another APA application that could take advantage of pore filling is its use as a substrate for living cell attachment and growth. In this case the largest possible pores are required (diameter≥300 nm), because cells could find better grasp on roughness features of this size **[7]**. Both bulk alumina and alumina zirconia ceramics are already used as implant materials for artificial joints, due to their excellent mechanical properties and wetting capability, which allows for effective lubrication **[1]**. Conversely, due to its porosity APA does not show the same favourable properties. However, proper pore functionalization could change this scenario.

Possible applications of APA in dentistry:

APA pores can be filled with any appropriate medium, e.g. cell nutrient solution and specific adhesion or growth factors such as proteins or peptides, and/or ions. Release of this content may be driven by environmental parameters such as temperature, pH, or concentration of synergically acting chemicals. In this way APA could be used to trigger cell adhesion and/or growth, and therefore influence tissue organization.

This functionalized APA may also be used as a scaffold for the generation of new tissue, which will be especially promoted by highly interconnected pores. This property can be achieved during industrial fabrication of APA by letting the pores arrange in an unstructured (or 'random') fashion, different from the laboratory-made 'ordered' APA required e.g. for optoelectronic devices. The high interconnectivity of pores in disordered APA makes this material a real 3D scaffold throughout its whole thickness.

APA thickness is typically lower than 100 µm, which makes APA not appropriate for the replacement of massive tissue. Furthermore, even the largest APA pores obtained so far are <1 µm in diameter, thus being a severe limitation for tissue vascularization **[8]**. Despite these limitations APA can be used as a coating of other non porous, passive, restorative filling materials, such as bulk ceramics or metal/metal alloys, an approach previously proposed for bioactive glasses **[9]**. In the case of APA, the pores can act as pinning points for the integration of the new tissue around the implant. This approach could be particularly effective if the pores are filled with protruding structures (e.g. collagen fibers) to mimic natural dentin, which has been shown to support material bonding **[10]**.

The proposed application requires a large inter-disciplinary effort: proteomics, genomic and bioinformatics/data-mining will be necessary to develop appropriate functionalization strategies, along with deeper understanding of APA wettability, and possibly lithographic patterning capabilities. Our multi-centric group is now exploring such a multi-faceted approach.

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Supplementary material:

Table 1: Possible applications of APA

	Application	Specific properties/problems
Biology/ Medicine	Purification of water/liquids from pathogens	Membrane form required, i.e. stand alone surface accessible from both sides, and bottom barrier layer opening via chemical wet etching.
	Scaffold for microarrays	Wettability issues. Top surface should be as flat as possible for controlled micro-spotting by e.g. contact printing pens.
	Biosensors/bioelectrodes	Thin film form required, for integration with technological microelectronics surfaces (silicon wafers, glass). Functionalization required with active (either sensitive or electrically conductive) layer.
	Substrate for cell adhesion and growth	Possibly large pores. No special requirements on either surface flatness or thickness.
Dentistry	Reservoir for the controlled release of growth factors and/or ions	Wettability issues. Filling with nanoparticles would require appropriate surfactant control.
	Scaffold for cell and tissue adhesion and growth	Large pores. No special requirements on surface flatness. Thin film form required for metal alloy implant coating.