Review

A review of adaptive mechanisms in cell responses towards oxidative stress caused by dental resin monomers

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A B S T R A C T

Dental composite resins are biomaterials commonly used to aesthetically restore the structure and function of teeth impaired by caries, erosion, or fracture. Residual monomers released from resin restorations as a result of incomplete polymerization processes interact with living oral tissues. Monomers like triethylene glycol dimethacrylate (TEGDMA) or 2-hydroxyethyl methacrylate (HEMA) are cytotoxic via apoptosis, induce genotoxic effects, and delay the cell cycle. Monomers also influence the response of cells of the innate immune system, inhibit specific odontoblast cell functions, or delay the odontogenic differentiation and mineralization processes in pulp-derived cells including stem cells. These observations indicate that resin monomers act as environmental stressors which inevitably disturb regulatory cellular networks through interference with signal transduction pathways. We hypothesize that an understanding of the cellular mechanisms underlying these phenomena will provide a better estimation of the consequences associated with dental therapy using composite materials, and lead to innovative therapeutic strategies and improved materials being used at tissue interfaces within the oral cavity. Current findings strongly suggest that monomers enhance the formation of reactive oxygen species (ROS), which is most likely the cause of biological reactions activated by dental composites and resin monomers. The aim of the present review manuscript is to discuss adaptive cell responses to oxidative stress caused by monomers. The particular significance of a tightly controlled network of non-enzymatic as well as enzymatic antioxidants for the regulation of cellular redox homeostasis and antioxidant defense in monomer-exposed cells will be addressed. The expression of ROS-metabolizing antioxidant enzymes like superoxide dismutase (SOD1), glutathione peroxidase (GPx1/2), and catalase in cells exposed to monomers will be discussed with particular emphasis on the role of glutathione (GSH), which is the major non-enzymatic antioxidant. The causal relationship between vital cell functions like the regulation of cell survival or cell death in monomer-treated cell cultures and the availability of GSH will be highlighted. We will also consider the influence of monomer-induced oxidative stress on central signal transduction pathways including mitogen-activated protein kinases (MAPK) ERK1/2, p38, and JNK as well as the stress-activated transcription factors downstream Elk-1, ATF-2, ATF-3, and cJun. Finally, we address signaling pathways originating from monomer-induced DNA damage including the activation of ATM (ataxia-telangiectasia mutated), Chk2, p53, p21, and H2AX. The understanding of the mechanisms underlying adaptive cell responses will stimulate a constructive debate on the development of smart dental restorative materials which come into contact with oral tissues and effective strategies in dental therapy.

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1. Introduction

Dental composite resins are prevalent materials used to aesthetically restore the structural integrity of teeth, generally impaired by caries, but also due to attrition, erosion, or fracture.

Hence, diverse resinous materials are available, for instance adhesives (primer and bonding agents), flowable and conventional composite resins, fiber-reinforced composites or resin cements [1,2]. Their therapeutic application depends on the depth, size, and location of the existing defect from fissure sealant, caries infiltration, direct and indirect restorative materials, endodontic sealer, post or retrograde root filling materials, and to luting agents for composite and ceramic restorations or orthodontic brackets [2—4]. Thus, following the revised definition of a biomaterial, dental

composite resins are considered materials which direct the course of dental therapy by the interaction with living systems [5].

Despite various modifications in the formulation, the chemical composition of composite resins include inorganic filler particles (quartz, ceramic or silicia), and additives which are incorporated into a mixture of an organic resin matrix [1,6]. The matrix of dental composites, based on methacrylate chemistry among others, contains strongly viscous major monomers like 2,2-bis[4-(2-hydroxy-3-methacrylyloxy-propoxy)phenyl] propane (Bis-GMA) or urethane dimethacrylate (UDMA), as well as dilutive monomers such as 2-hydroxyethyl methacrylate (HEMA) or the comonomer triethylene glycol dimethacrylate (TEGDMA) (Fig. 1) [1,7,8]. Physical and chemical properties as well as the clinical performance of composite materials depend on adequate polymerization of resin monomers. Since monomer-polymer conversion is never complete, mechanical properties and wear performance of composites may decline in a clinical situation. Moreover, a low degree of conversion leads to the release of unbound residual monomers into the oral environment and leaves composites susceptible to biodegradation [9–13]. For this reason, dental composite materials are a lasting source of bioactive compounds in various tissues of the oral cavity in both short- and long-term scenarios.

A meta-analysis on the quantities detected in eluates of multiple composite filling materials predicted that resin monomers in the nanomolar range would likely be disposable from the composite into its aqueous environment [14]. Apart from clinically observed contact allergies, results from in vivo studies suggested that amounts of monomers released from dental composites were far below levels required to cause systemic adverse effects [15]. These observations, however, have only limited significance with respect to local exposure of, for instance, the dentin–pulp complex to composite materials since the use of adhesives, which are almost exclusively composed of monomers, is mandatory prior to the use of a composite filling material. Not surprisingly, inflammation or inhibition of dentin mineralization has been reported when composite materials were applied in direct contact to dental pulp tissue [16–18].

Based on in vitro cell culture experiments of multiple target cells, resin monomers were detected to specifically interfere with various vital cellular functions [19,20]. Interestingly, there is experimental evidence showing that uptake, and thus the actual intracellular concentration of resin monomers causing adaptive cell responses, is more than ten times lower than the extracellularly available concentration [21]. Resin monomers like TEGDMA or HEMA-induced cytotoxicity via apoptosis in various cell types including pulp and gingiva cells, and genotoxic or mutagenic effects caused by monomers were reported as well. Most likely as a result of monomer-induced DNA strand breaks, mammalian cells activate functional cell cycle checkpoints through the coordinated activities of regulatory proteins [22–24]. Monomers also influenced specific cell responses of the innate immune system. TEGDMA and HEMA instantaneously downregulated LPS-induced cytokine production in macrophages and inhibited the expression of surface antigens like CD14 and other surface markers essential for the controlled interaction of immune cells [25–27]. Furthermore, low TEGDMA concentrations and chemically related substances like PMMA (poly-methyl methacrylate) even inhibited specific odontoblast functions including alkaline phosphatase activity, the matrix mineralizing capability, calcium deposition, and gene expression such as dentin sialoprotein [28,29]. Moreover, physiologically relevant levels of resin monomers significantly delayed odontogenic differentiation and mineralization processes in pulp-derived cells including stem cells, most likely with serious consequences for physiological dentine repair or developmental processes of human permanent teeth [29–33].
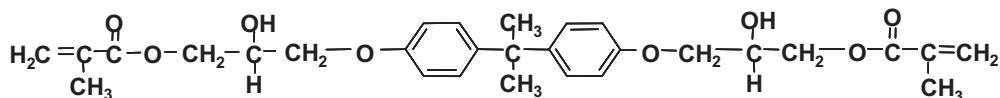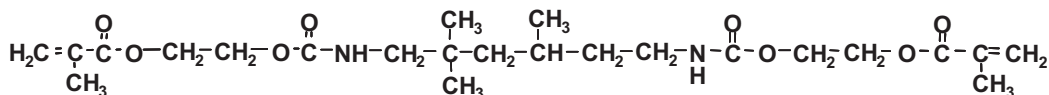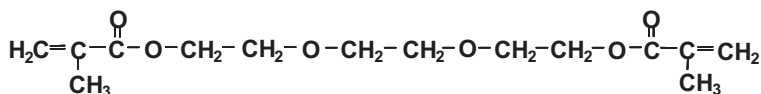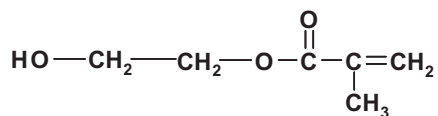

Fig. 1. Chemical structures of major monomers of dental resin materials.