



Responsiveness of human monocyte-derived dendritic cells to thimerosal and mercury derivatives

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ABSTRACT

Several cases of skin sensitization have been reported following the application of thimerosal, which is composed of ethyl mercury and thiosalicylic acid (TSA). However, few *in vitro* studies have been carried out on human dendritic cells (DCs) which play an essential role in the initiation of allergic contact dermatitis. The aim of the present study was to identify the effect of thimerosal and other mercury compounds on human DCs. To address this purpose, DCs derived from monocytes (mono-DCs) were used. Data show that thimerosal and mercury derivatives induced DC activation, as monitored by CD86 and HLA-DR overexpression associated with the secretion of tumor necrosis factor α and interleukin 8, similarly to lipopolysaccharide and the sensitizers, 1-chloro-2,4-dinitrobenzene (DNCB) and nickel sulfate, which were used as positive controls. In contrast, TSA, the non-mercury part of thimerosal, as well as dichloronitrobenzene, a DNCB negative control, and the irritant, sodium dodecyl sulfate, had no effect. Moreover, oxidative stress, monitored by ROS induction and depolarization of the mitochondrial membrane potential, was induced by thimerosal and mercury compounds, as well as DNCB, in comparison with hydrogen peroxide, used as a positive control. The role of thiol oxidation in the initiation of mono-DC activation was confirmed by a pre-treatment with *N*-acetyl-L-cysteine which strongly decreased chemical-induced CD86 overexpression.

These data are in agreement with several clinical observations of the high relevance of thimerosal in patch-test reactions and prove that human mono-DCs are useful *in vitro* tools for determining the allergenic potency of chemicals.

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Introduction

Thimerosal, which is also called merthiolate or thiomersal in clinical assays, is an organomercury product composed of ethyl mercury (EtHgCl) and thiosalicylic acid (TSA). Due to its antimicrobial properties, thimerosal is frequently found in topical antiseptic solutions and ointments. It is widely used as a preservative in vaccines, ophthalmic products and cosmetics (for a review, see Geier et al., 2007). Since the last decade, many cases of cutaneous reactions and skin sensitization in atopic children have been reported (Zenarola et al., 1995; Goncalo et al., 1996; Patrizi et al., 1999; Suneja and Belsito, 2001). Recently, statistical overviews of long-term trends in patch-test reactions in several countries reported large patch-test studies that reflected the high reactivity of thimerosal which was classified as the second most common allergen after nickel (Goon and Goh, 2006; Wattanakrai and Rajatanavin, 2007; Tudela et al., 2008; Cheng et al., 2008; Hammonds et al., 2009). However,

the clinical relevance of thimerosal is still under discussion (Belsito, 2002; Slodownik and Ingber, 2005; Breithaupt and Jacob, 2008) and is currently pertinent as thimerosal is still added in several types of vaccines such as influenza A(H1N1), diphtheria toxoid, acellular pertussis and tetanus toxoid (www.afssaps.fr; www.eurosurveillance.org; www.fda.gov; www.vaccinesafety.edu). However, only few investigations were targeted on thimerosal effect towards the immune system. The effect of thimerosal has been studied mostly in rodents where a toxic reaction and some cases of autoimmunity were reported (Havarinasab et al., 2004; Silbergeld et al., 2005). Investigations on Jurkat T cell line have shown that thimerosal was able to induce apoptosis (Makani et al., 2002) and confirmed the sensitivity of T cells to thimerosal (Lee-Wong et al., 2005). Only recent studies (Goth et al., 2006; Agrawal et al., 2007) have demonstrated a direct effect of thimerosal on human dendritic cells (DCs), which play an essential role in the immune response and in the initiation of allergic contact dermatitis.

Several studies reported that immature DCs are generated *in vitro* from human monocytes (mono-DCs) and acquire a mature phenotype after 48 h exposure to sensitizers as previously described for 1-chloro-2,4-dinitrobenzene (DNCB) and nickel sulfide (NiSO₄) whereas non-sensitizers such as SDS had no significant effect (Aiba et al., 1997; Coutant et al., 1999; Guironnet et al., 2000; Tuschl et al., 2000; Hulette

Abbreviations: DCs, dendritic cells; mono-DCs, DCs derived from monocytes; NAC, *N*-acetyl-L-cysteine; ROS, reactive oxygen species; TSA, thiosalicylic acid.

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