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The influence of pH and concentration of mucins on diesel exhaust particles (DEPs) transport through artificial mucus

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ABSTRACT

Mucus layer is the first line of defense for the innate immune system. The mucus function is closely associated with its components and physicochemical and rheological properties. From the rheological point of view mucus is a highly non-Newtonian, thixotropic, viscoelastic material. The changes in mucus' composition, its properties as well as glycosylation process which develops with age and depends on environmental and health conditions lead to rheological changes.

Due to the complexity of mucus' structure and possible defensemechanisms, it is very important to determine the effects of various factors, including various types of particles, drugs, microorganisms etc. on mucus' functions. In this study we focused on diesel exhaust particles (DEP) and their interaction with mucus.

The results show that the transport of soot aggregates through mucus is affected not only by mucus' apparent viscosity. It is also possible that the interaction between the DEPs, their surface type, and the components of mucus strongly influence transport as well as the mucins' concentration and the pH level.

1. Introduction

Mucus layer is, just like skin, the first line of defense for the innate immune system. The main role of mucus, regardless of its location, is to form a layer preventing the epithelial cells from being invaded by exogenous particles, pathogens and toxins. The mucus' function is closely associated with its components and physicochemical and rheological properties. In general, mucus consists of water (95%), mucins – the main dry weight component (2–5% [w/v]), lipids (~1%), minerals (~1%) and DNA (~0,02%) (Quaraishi, Jones & Mason, 1998). The more detailed composition of mucus still remains unknown and varies depending on the place of mucus' secretion. Mucin glicoproteins are considered to be major components which reduce diffusion through mucus. Fibers of mucin are in a size range of 10-40 MDa and 3–10 nm of diameter (Lai, Wang, Wirtz & Hanes, 2009a). They are crosslinked, connected and arranged in a network which may play an important role in mucus' barrier properties. From rheological point of view mucus is a highly non-Newtonian, thixotropic and viscoelastic material. The changes in mucus composition, its properties and glycosylation process which develops with age and depends on environmental and health conditions lead to rheological changes. For example, acidic pollutants have been shown to reduce mucus viscosity (Holma & Hegg, 1989). Smoking also causes reduction of viscosity (Kollerstrom et al., 1977), while

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addition of immunoglobulines A, M (IgA, IgM) leads to anincrease in viscosity (Girod, Zahm, Plotkowski, Beck & Puchelle, 1992).

Generally, mucus rheology and its properties are controlled by concentration of mucine and other glycoproteins, jonic, lipids, water content and pH. In diseases like cystic fibrosis, the decrease in water and increase in mucins secretion raise mucus viscoelastisity (Boucher, Cotton, Gatzy, Knowles & Yankaskas, 1988). When pH of mucus decreases the viscoelastisity increases. Reduction of pH level results in protonation of the carboxylates' group of the amino acids which leads to rupture and exposure of the salt bridge groups and glycosylation of amino acids increasing the cross-linking of mucins (Bansil and Turner, 2006). The degree of cross-linking of mucins also affects the size of pores between mucins' fibers. The size of pores of native respiratory mucus is in the range of between $\sim$100 nm to several micrometers (Kirch et al., 2012), while the pore diameter of acidic mucus is 340 ± 70 nm (Lai, Wang, Hida, Cone & Hanes, 2010).

The pH level of respiratory mucus is about 7, so the protective function may be weakened in comparison with acidic mucus. On the other hand, low mucus viscoelasticity allows effective mucocilliary transport, which is also an important element of mucus barrier properties. However, when pH of mucus is around 7 or higher, transport of charged and neutral particles is not limited. Lai et al. (2009b) showed that negatively charged Human Immunodeficiency Virus Type 1 (HIV) is trapped by acidic mucus, by not by neutral mucus. Charged micron-sized particles are stopped by low pH mucus, but neutral particles may freely diffuse.McGill and Smyth (2010) found that some particles, such as inhaled pollutants, environmental aerosols and drugs may interact with biopolymers presented in mucus. Inhaled particles deposited in mucus can adsorb mucins' fibers on their surface, increasing the local density of mucus and also contributing to the increasing diameter of pores in mucus which may result in its higher permeability. In conclusion, mucus has multiple barrier properties, but various factors can affect their actual efficacy.

Boegh and Nielsen (2015) classified the mechanisms of mucus protection into three categories: dynamic, steric, and interactive barrier. The dynamic barrier is created by continuously secreted mucus. The steric barrier is created by cross-linking of mucins' fibers. The mucins' fibers may form a type of filter effectively holding off exogenous particles or molecules. The interactive barrier is created by interactions (hydrophobic, hydrogen bond, ionic, adsorption) of particles, molecules, viruses etc. () with mucus' components. All those mechanisms coexist and jointly determine mucus' multiple barrier properties.

Due to the complexity of mucus' structure and possible mechanisms of protection, it is very important to determine the effects of various factors, different particles, drug, microorganisms etc. on mucus' functions. In the study we focused on diesel exhaust particles and their interaction with mucus.

The diesel engine is considered to be the major emitter of particles in the air (diesel exhaust particles – DEPs). Fine particles can easily be inhaled into the respiratory system, but the mucus covering the respiratory tract should be the barrier protecting human body against them. Although the rheological properties of mucus have recently been the subject of multiple research, less information is available about its properties as a diffusion barrier affecting transportation of aggregates (especially DEPs aggregates). Even though the impact of DEPs aggregates on various structures has been extensively investigated, there is still not enough information about the influence of DEPs aggregates' morphology on human health.

In 2015, 52.1% of all newly registered cars in Western Europe were equipped with diesel engine (ACEA, 2016). This trend has been nearly constant since 2006 (excluding 2009 – 45.9%). The Euro 5 emission standard (effective from 2009 for passenger cars and light commercial service) reduced the number of particles generated by the engines to 5 mg/km. It also imposed an obligation to use diesel particulate filter (DPF) in all new diesel cars. DPF reduces number of emitted DEPs aggregates even up to 99% (Ulrich et al., 2012). Additionally, the morphology, as well as physical and chemical properties of DEPs from diesel engines equipped with DPF, may be different from those without DPF. However, the average age of a car in the European Union is 9.65 years (ACEA, 2016), so there still is a considerable number of vehicles without DPF. Moreover, high repair cost of DPF results in them being often dismantled. In the light of the above, we are still exposed to particles from diesel exhausts, even though the particle filters in engines have been in use since the nineties. Therefore, not only the employees of the depots or garages are exposed to diesel exhausts, but also all the habitants of large cities or, simply, all road users.

Diesel exhaust fumes are a complex mixture of gas phase and particles' phase. IARC (International Agency for Research on Cancer) classified diesel exhaust as carcinogens to humans. Particles produced by diesel engines are the result of an incomplete combustion of fuel. The particles' phase mainly consists of fine particles with elemental carbon core. DEPs are aggregates of primary particles with various compounds adsorbed on their surface (e.g. organic compounds, mostly PAHs (polycyclic aromatic hydrocarbons), sulfate and metallic ash (Maricq, 2007)). Typical composition of the DEPs consists of elementary carbon in the amount of about 20% of the particle mass (Kittelson, 1998) and the organic compounds, oil, sulfur, ash, etc. in the amount of 80% of the particle mass (Ono-Ogasawara et al., 2004). Diameter of the aggregates is in the range 10 nm – 600 nm, however most of the particles have the diameter of 100 nm (Kittelson, 1998; Harris et al., 2001). Size, surface, adsorbed substances and emissions of DEPs strongly depend on the composition of fuel and are different for engines operating on diesel oil, biodiesel oil and sulfur-free diesel oil (Krahl, Munack, Schröder, Stein & Bünger, 2003). Condition of an engine, its load, age and additional equipment also impact formation of particles (Su et al., 2004; Burtscher, 2005).

Fine aggregates (< 1000 nm) can be inhaled and deposited into the lungs. Our earlier research (Penconek et al., 2013) indicated that the differences in morphology of the DEPs aggregates influence the differences in deposition of aggregates in human respiratory tract model. In addition, the research indicated that irrespective of the type of fuel, a higher amount of