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Interaction Between Surfactin and U-937 Human Macrophages: Cytotoxicity, Reactive Oxygen Species Content, Mitochondria Membrane Potential, Cell Cycle Profiles, and *in vitro* Proteolytic Stability

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Surfactin is a biosurfactant widely used in biomedical applications; however, information on its biocompatibility and stability in humans is limited. Surfactin is hemolytic, and because it is a peptide, its *in vivo* proteolytic stability must be validated for use in humans. Similar to particulate foreign bodies, surfactin is captured primarily by the human mononuclear phagocyte system. The interactions between surfactin and macrophages are important because macrophages are central in the host defense system and provide opportunities for evaluating the cytotoxicity of surfactin. Hence, we examined the changes in human macrophages (U-937 cells) after they had been treated with surfactin: their dehydrogenase activity, an indicator of cell viability, and their intracellular responses- reactive oxygen species content, mitochondrial membrane potential, and cell cycle profiles- were assessed. The *in vitro* stability of surfactin was analyzed using MALDI-TOF (matrix-assisted laser desorption and ionization with time-of-flight mass spectrometry. Surfactin had dose-dependent toxic effects on U-937 cell viability and damaged surfactin-treated HeLa (human cervical cancer) and NIH/3T3 (mouse fibroblast) cells. Hydrogen peroxide production in surfactin-treated macrophages was unstable. However, superoxide anion content significantly increased relative to that in untreated control cells over the incubation times (0.5 and 1 h). Mitochondrial membrane potential rose dose-dependently relative to that in untreated control cells, except for significant increases at a dose of 5 μM. Apoptosis developed at higher doses after 4 h of incubation at 10 μM. Surfactin was stable for ~24 h of incubation. Our findings may provide a better understanding of the action of surfactin in humans.