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Tim4, a macrophage receptor for apoptotic cells, binds polystyrene microplastics via aromatic-aromatic interactions

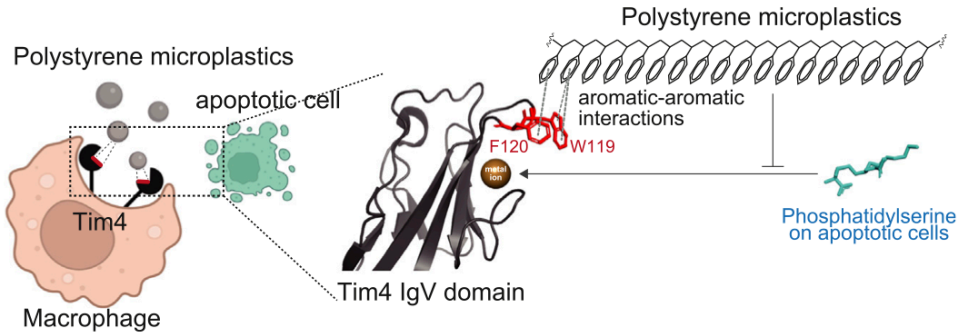
Miki Kuroiwa [a,1], Shin-Ichiro Yamaguchi [a,1], Yoshinobu Kato [a], Arisa Hori [a], Saori Toyoura [a], Mai Nakahara [a], Nobuyuki Morimoto [b], Masafumi Nakayama [a,*]

[a] Laboratory of Immunology and Microbiology, College of Pharmaceutical Sciences, Ritsumeikan University, Kusatsu, Japan
[b] Department of Materials for Energy, Shimane University, Shimane, Japan

HIGHLIGHTS

- Tim4 binds polystyrene (PS) microplastics via aromatic-aromatic interactions.
- Tim4 is involved in macrophage engulfment of PS microplastics.
- PS microplastics do not stimulate macrophages to produce inflammatory cytokines.
- PS microplastics perturb Tim4-mediated efferocytosis.

GRAPHICAL ABSTRACT



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ABSTRACT

Understanding the interface between microplastics and biological systems will provide new insights into the impacts of microplastics on living organisms. When microplastics enter the body, they are engulfed preferentially by phagocytes such as macrophages. However, it is not fully understood how phagocytes recognize microplastics and how microplastics impact phagocyte functions. In this study, we demonstrate that T cell immunoglobulin mucin 4 (Tim4), a macrophage receptor for phosphatidylserine (PtdSer) on apoptotic cells, binds polystyrene (PS) microparticles as well as multi-walled carbon nanotubes (MWCNTs) through the extracellular aromatic cluster, revealing a novel interface between microplastics and biological systems via aromatic-aromatic interactions. Genetic deletion of Tim4 demonstrated that Tim4 is involved in macrophage engulfment of PS microplastics as well as of MWCNTs. While Tim4-mediated engulfment of MWCNTs causes NLRP3-dependent IL-1β secretion, that of PS microparticles does not. PS microparticles neither induce TNF-α, reactive oxygen species, nor nitric oxide production. These data indicate that PS microparticles are not inflammatory. The PtdSer-binding site of Tim4 contains an aromatic cluster that binds PS, and Tim4-mediated macrophage engulfment of apoptotic cells, a process called *efferocytosis*, was competitively blocked by PS microparticles. These data suggest that PS microplastics do not directly cause acute inflammation but perturb efferocytosis, raising concerns that chronic exposure to large amounts of PS microplastics may cause chronic inflammation leading to autoimmune diseases.

1. Introduction

Global production of plastics is estimated to be 400 million tons per year, approximately half of which is used as single-use packaging, thus resulting in plastic waste (MacLeod et al., 2021; Wright and Kelly, 2017). In the environment, most plastics are not biodegradable and become brittle

* Corresponding author at: Laboratory of Immunology and Microbiology, College of Pharmaceutical Sciences, Ritsumeikan University, 1-1-1 Noji-Higashi, Kusatsu, Shiga 525-8577, Japan.
E-mail address: mnakayam@fc.ritsumei.ac.jp (M. Nakayama).
[1] Contributed equally.

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