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Macrophages: Checking toxicity of fungal metabolites in the colon

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Abstract

It is well known that the intestine absorbs nutrients, electrolytes and water. Chikina *et al.* recently demonstrated that it is also able to sense, recognize and block the absorption of toxins through a very sophisticated interactive cellular cooperation between novel subpopulations of macrophages and epithelial cells.

Main text

Although epithelia line the entire internal body and are continuously exposed to microorganisms, epithelial cells (ECs) are rather considered as the minions of the king macrophage in terms of host defense against microbial pathogens. The recent work of Chikina *et al.* restores an historical truth in the immunology landscape. The authors have characterized a subepithelial population of distal colon macrophages, forming “balloon-like protrusions” (BLPs) between ECs [1]. These colonic macrophages (CMs) sample and examine fluids absorbed by distal colon ECs and instruct them to stop fluid absorption, if toxic fungal metabolites are present. Depletion of macrophages resulted in massive apoptosis of ECs, together with a marked increase in barrier permeability in the distal but not proximal colon when CMs were absent. Membranes and vesicles from epithelial origin were found within the BLPs. BLPs themselves were positive for late-endosomal/lysosomal markers suggesting that the signal is not the toxin itself but the ghost of the dead ECs. Whole mount immunostaining of colon sections as well as single cell RNA sequencing brought to suspect a role of the microbiota in the emergence of BLPs. Surprisingly, the use of antifungals and antibacterial compounds as well as colonizing assays of germ-free mice devoid of BLP⁺ CMs, with a bacterial mix or the commensal fungus *Candida albicans*, resulted only in an initially strong BLP formation when *C. albicans* was introduced and caused EC death. As a conclusion, the mycobiota was recognized as the only responsible causative agent of the formation of BLPs. Since fluid absorption in the distal colon is achieved by ECs, BLPs contain membrane fragments and vesicles of ECs and in absence of recognition of cell wall components by host C-type lectins, the authors conclude that BLP⁺ CMs could sample soluble fungal toxins or metabolites. Indeed, BLP-formation was increased while absorption was stopped when gliotoxin, that is known to induce apoptosis in ECs, was present. Moreover, the macrophage deficient CD64^{DTR} mice did not stop absorption of gliotoxin resulting in massive apoptosis of ECs, confirming that BLP⁺CMs mediate toxin recognition and absorption stop. With these elegant experiments, the role of BLP⁺CMs as immune sentinels controlling fungal toxin intake and protecting EC was unraveled.

This enlightening article opens several questions and new exciting research avenues. First, are these cellular events elucidated in mice also occurring in humans? Moreover, is the amount

of toxins used by the authors fitted to *in vivo* concentrations of the toxic molecules in the distal colon? The fact that the three fungal molecules used belong to different chemical families suggests that the chemical nature of the toxins is not important but rather its toxicity. However, the toxins used are quite “weak” toxins and it would be of interest to investigate if deadly/lethal toxins, like *bacterial Botulinum* toxin, *Staphylococcus* toxins, or fungal phalloidin, are sensed by the same cellular cooperation. In addition, molecular mechanisms engaged in the recognition of fungal toxins by BLP⁺ CMs remain obscure: are we dealing with more sophisticated sensing systems than the scavenging mechanisms of macrophages dealing with dead epithelial cells? Is this cellular cooperation only found in the colon or can it occur in other body parts?

The lung epithelium is the largest surface in contact with the outside environment being in permanent contact with pathogenic microorganisms and their innocuous molecules by respiring daily more than 10.000 liters unsterile air. In the lung, cross talks between macrophages and ECs have been demonstrated [2]. Despite the different physiological roles of gut and lung epithelium, both compartments consist of mucus- or surfactant-covered single-layer epithelia being in charge of fluid absorption or gas exchange, respectively. Both epithelia need protection against invading microorganisms and their toxic metabolites. If the role of the usual allergenic microorganisms has been repeatedly shown, the sensing of inhaled toxic molecules has not been assessed in the lung. As emphasized by Chikina *et al.*, the understanding of putative cooperation between ECs and macrophages to sense toxins can only be investigated *in vivo* in the tissue context. Novel insights for CM counterparts, alveolar macrophages (AMs), in the lung were recently gained. The role of extracellular vesicles in the exchange of cargo molecules (metabolites, proteins, RNAs or microRNAs) has been recently demonstrated. If these extracellular vesicles have been shown to regulate and facilitate cross talks between ECs and AMs, their impact only begins to be understood [3,4]. The CD11c^{high} AM subpopulation was recently characterized which displayed functional dynamics based on the CXCL2 chemoattractant expression in response of fungal infections [5]. A long-existing conundrum regarding AMs was also recently solved: AMs were thought to be immotile, but three alveoli share one AM assuming two thirds of the alveoli would be unprotected. Elegant studies, using system biology approaches or intravital lung imaging combined with a labeling

approach exploiting AMs critical function-constant phagocytosis, could show that AM are patrolling in between the lung epithelium through pores of Kohn and actively crawl towards bacterial and fungal pathogens and that viral infections impair AM migration [6,7]. The analysis of Cx43⁺ populations demonstrated that gap junction channels between AMs and ECs use Ca²⁺ waves for cell communication, especially between AT1 and AT2 ECs [8,9]. Although mycotoxins have been shown to be able to disrupt cellular integrity by harming mitochondrial, attenuating mucus layers or imbalancing inflammatory factors, the role of macrophages and ECs cross talks have not been assessed in sensing mycotoxins. The existence of multiple toxic secondary metabolites produced by *Aspergillus fumigatus*, a common inhabitant and lung pathogen or other food borne inhaled toxins, could also be a way to investigate the specificity of each toxin family in the lung epithelium. Moreover, the interactions between the mycotoxins and innocuous allergens, antigens or the microorganism itself have neither been investigated by Chikina *et al.*, nor in the lung. The recent discovery of the cellular interactions in the distal colon could also introduce a way to investigate putative long distance talks along the gut-lung axis identified in several microbiota studies for example regarding sepsis or cystic fibrosis patients [10].

Together, these original findings highlight so-far unexpected specialized features of macrophages in close contact with ECs to maintain homeostatic functions, tissue integrity and in turn control and counteract invading pathogens directly or indirectly in a more and more complex every day at the scale of an individual.

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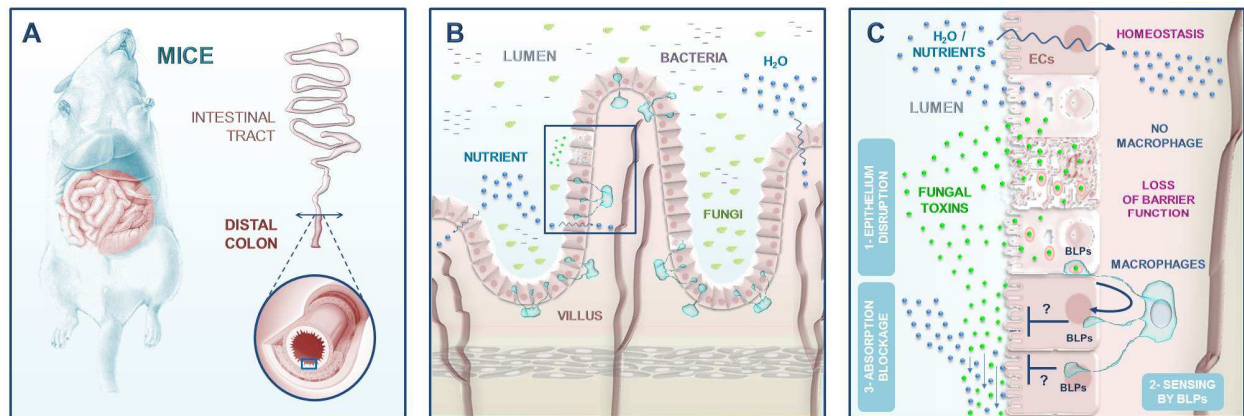


Figure 1. Macrophages maintain colonic epithelium integrity by limiting fungal toxins absorption. **A.** Experiments were conducted taking mouse distal colon as epithelium model. **B.** The intestinal epithelium acts as a selectively permeable filter that allows the absorption of nutrients, electrolytes, and water, which can then reach the blood circulation for organ irrigation. Because of this primarily function, the colonic mucosa and its associated immune system are constantly exposed to foreign antigens and metabolites, which for the most part should be tolerated. In this respect, the fungal component of the microbiota, i.e. the mycobiota including mainly yeasts such as *Candida albicans*, is well known to play a crucial role in regulating the host gut homeostasis. **C.** Accumulating evidence suggests that fungal communities that are enriched in the distal segment of the colon release a broad series of metabolites that are toxic to epithelial cells (ECs), promoting barrier disruption. Here, authors have characterized a sub-epithelial population of distal colon macrophages, forming “balloon-like protrusion” (BLPs) between ECs. These colonic macrophages sample and examine fluids absorbed by distal colon ECs and instruct them to stop fluid absorption, if toxic fungal metabolites are present.