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Editorial Open Access

The Immune System uses iTregs to keep from giving Non-pathogenic Microorganisms a "Time-Out"

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I am not sure how it is in your household, but the hours in between picking the kids up from school to bedtime are some of the most hectic hours of the day. It is funny, but as the kids become more tired from the many activities of the day, it seems the less likely they are to do what they are told. Therefore, (as its already known by many reading this editorial) there comes a time-point when (often after tripping over the scooter that you asked the kids to move four earlier times) you must decide whether to put the kids into "time-out" to reinforce the fact that they need to listen, or just send them to bed because they are tired. If a punishment is necessary, it must be appropriate to the offense. In addition, there are times when overlooking the transgression is most important. Oftentimes my decisions are based on one fact- they are children and they are only doing what children do. In analogous fashion the mammalian immune system must make a decision of whether a microorganism is indeed a pathogen (and capable of causing disease), or is simply doing what micro-organisms do occupying free space in search of food. In this editorial within Air and Water Borne Diseases, we will take notice that the majority of microorganisms that we encounter from air and water are not pathogens, and briefly focus on why it is important that the immune system generates regulatory T cells to prevent "active correction" of microorganisms that are not pathogenic.

It is 7:45 at night, and as we are watching the end of "Dora", a transgression is committed by one of the kids. Sometimes, 1) because we ourselves don't want to expend the energy (we had a long day in the lab or hospital) or 2) because they are our children (and thus a part of us), we choose to ignore the transgression and finish watching "Dora" before going to bed. In analogous fashion it is likely that our immune system sometimes chooses to actively ignore the presence of non-pathogenic microorganisms. There is an overabundance of microorganisms everywhere, many of which we encounter every time we breathe or have a bite to eat. Closer to home, there are 10 x more bacterial cells associated with our bodies than human cells [1], suggesting complex interplay between ourselves and our associated bacteria. If our immune systems chose "to actively correct" all the microorganisms that we encounter daily basis through elimination, then diseases which are based on excessive inflammatory states, such as tuberculosis or inflammatory bowel disease would likely be far more common. Moreover, significantly more energy would have to be invested in defense against microorganisms that are not pathogenic, but rather simply doing what microorganisms do. It appears that one manner in which our immune system chooses to actively ignore is through the generation of regulatory T cells (Treg). In recent years, the Treg has become one of the most widely studied immune cell subsets, due largely to its ability to moderate excessive inflammation (immune responsiveness) [2]. The most readily studied variety of Tregs, identified through the presence of the transcription factor Foxp3, comes in two varieties: the naturally occurring (nTreg) and the induced (iTreg). nTregs are thymically generated (express Foxp3 in the thymus), bear a strong T Cell Receptor (TCR) specificity to self-peptides, and play a critical role in the prevention of aberrant immune responses directed against self-tissues [3]. In contrast, the iTreg is derived in the periphery from naive conventional cells that are converted to express Foxp3 in the presence of the cytokine TGF and TCR stimulation [4]. Notably, iTregs, since they are derived from naive conventional T cells, do not share the nTreg constraint of bearing TCR specificity to self-antigens. The TCR specificity of iTregs, rather, can be directed towards non-self antigens such as leishmania [5], or even resident gut flora [6]. These pieces of recent evidence suggest that, as it is well accepted that nTregs play a critical role in the regulation of excessive immune responses directed against self-tissues, it is likely that iTregs play a significant role in the prevention of excessive immune responses directed towards microorganisms that have co-evolved with us over the years. In essence, the generation of iTregs bearing a TCR with specificity to various microbes is analogous to parents choosing to not respond to a transgression committed by the children near bedtime. In this way the immune system does not expend excessive energy on non-pathogenic organisms, which may actually perform beneficial services.

Although other mechanisms to prevent excessive immune responses to gut flora exist, including the production of bacteria specific IgA and the sequestering of bacteria by innate immune responses, the induction of Tregs bearing TCR specificity for microbial antigens undoubtedly plays a critical role in the prevention of excessive immune responses directed against commensal flora. Thankfully for us, it appears that the immune system has made the decision that sometimes it is better for all parties involved to just go to bed without incident.

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