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Life-Saving Degeneracy in the Human Immune System

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Different human immune system components coordinate to ensure effective control of pathogens. Israel et al. (2017) examine the immune system of a patient with an inborn genetic error, presenting as impaired TLR signaling and staphylococcal disease, and uncover a beautiful example of degeneracy between innate and adaptive branches of immunity.

Complex adaptive systems are characterized by multiple different components interacting and giving rise to behaviors by the system as a whole, which are not predictable from observations of individual components alone (Holland, 2006). The vertebrate immune system is a prototypic complex adaptive system with cells and proteins interacting to coordinate systems-level responses. The system is also adaptive in nature, learning from past experiences and responding more vigorously to re-challenges. Another characteristic of many complex adaptive systems is the presence of redundant and degenerate components. While redundancy is the ability of structurally identical components to perform similar functions, degeneracy refers to an ability of structurally different system components to perform similar functions (Tononi et al., 1999). These properties can ensure robustness in complex systems, defined as the ability of a system to maintenance-specific functional properties, when faced with internal or external perturbations (Kitano, 2004). In "immunospeak," this means maintaining the ability to respond to an infectious agent "X" even after overcoming an infection by a disparate pathogen "Y." Obviously, we wouldn't survive without this kind of immunological robustness.

With these concepts in mind, it is worth discussing a recent report from Israel et al. (2017), in *Cell*. Israel et al. (2017) report on an elegant example of immunological degeneracy involving both innate and adaptive arms of the human immune system. After encountering a young patient with life-threatening staphylococcal disease and identifying this patient as a carrier of an autosomal recessive TIRAP deficiency previously not described, Israel et al. (2017) went on to analyze the family members of the patient. Surprisingly, seven additional family members were similarly homozygous for the same mutation but never presented with symptoms of immunodeficiency in general and severe Staphylococcal disease in particular (Israel et al., 2017). Incomplete penetrance of monogenic disorders is well known, but the underlying molecular explanations are often unknown. Remarkably, Israel et al. (2017) were not only able to pinpoint the functional defect in TIRAP-deficient individuals as an impaired TLR1/2, TLR2/6, and TLR4 signaling upon stimulation, but also explain the penetrance to the proband (i.e., the initial family member studied), but not to her family members. When comparing responses to the staphylococcal lipoteichoic acid (LTA), a TLR2/6 ligand, only the proband was unable to respond and, correspondingly, was the only family member lacking LTA-specific antibodies (Figure 1) (Israel et al., 2017). Although not formally proven, it is conceivable that Fc receptor-mediated responses to LTA, dependent on LTA-specific antibodies, are responsible

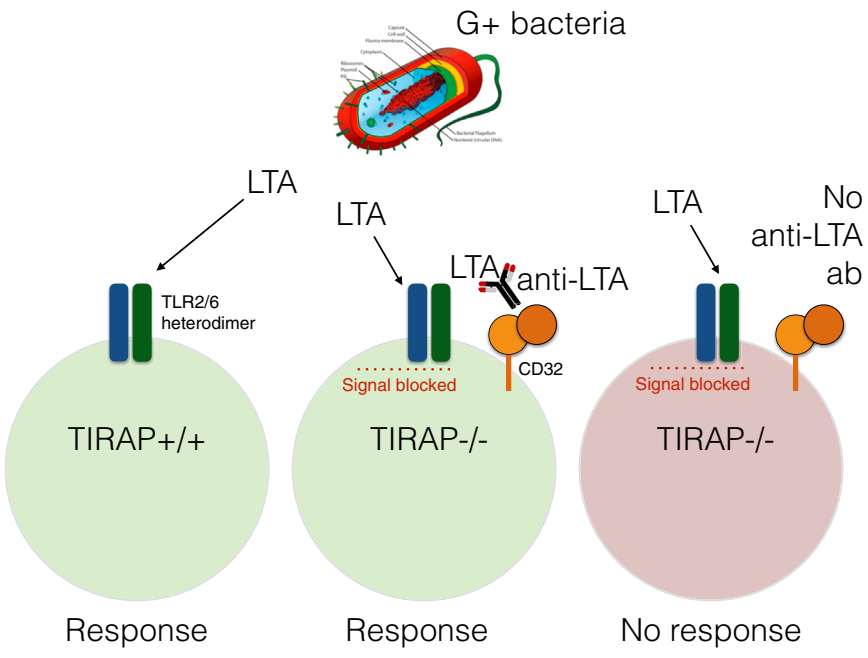

Figure 1. Adaptive LTA-Specific Antibodies Rescue Deficient TLR Responses to LTA in TIRAP-Deficient Individuals
In TIRAP+/+ individuals, responses to LTA signal via TLR2/6 and possibly also via CD32 if LTA-specific antibodies are present (left). If TIRAP is deficient, normal TLR2/6-mediated responses are deficient but can be rescued by the simultaneous signals mediated via CD32 binding of the Fc-region of LTA-specific antibodies (middle). In the absence of LTA-specific antibodies, TIRAP−/− individuals fails to mount any response to LTA and the patient is susceptible to severe infection (right).

for the rescue in these TIRAP-deficient family members, but not in the proband, who lacks such antibodies (Figure 1). CD32-mediated responses have previously been shown to potentiate responses to LTA, supporting this notion (Bunk et al., 2010). The work of Israel et al. (2017) shows that adaptive responses, in this case to the bacteria Staphylococcus, can rescue an inborn error of innate immunity and provide an explanation for the incomplete penetrance of the disease in this family. The structurally different responses to LTA, involving direct recognition of this factor by TLR2/6 and Fc-mediated responses dependent on LTA-specific antibodies, also represent an elegant example of immunological degeneracy ensuring robustness and survival.

The work of Israel et al. (2017) continue a long stream of elegant studies, from the Casanova laboratory and others, showing genetic susceptibility to infectious diseases (Casanova, 2015). In some cases, the findings in humans differ from the results of knockout mice (Qin et al., 2004), illustrating the importance of studies performed directly in humans (Davis, 2008).

The function and composition of human immune systems are incredibly variable between individuals, yet quite stable within individuals over time (Brodin and Davis, 2016). As we learn more about the influences that shape a given individual's immune system (Brodin et al., 2015), keeping the principles of robustness, redundancy, and degeneracy in mind will help us interpret the observations made by considering them in the light of general organizing principles of complex adaptive systems.

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A Feast of Malaria Parasite Genomes

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The *Plasmodium* genus has evolved over time and across hosts, complexifying our understanding of malaria. In a recent *Nature* paper, Rutledge et al. (2017) describe the genome sequences of three major human malaria parasite species, providing insight into *Plasmodium* evolution and raising the question of how many species there are.

A budding malariologist in the 1990s was steeped in the dogma that there were four species of malaria parasite responsible for millions of cases of malaria in tropical and sub-tropical regions of the world. *Plasmodium falciparum* was the deadliest, causing two to three million deaths each year due to the development of cerebral malaria in children under the age of 5 in sub-Saharan countries. *Plasmodium vivax*, on the other hand, was the comparatively "benign" species found in South American and Central and Southeast Asian countries, little studied because of the greater threat posed by *P. falciparum* and the lack of an in vitro culture system. *Plasmodium malariae* and *Plasmodium ovale* were species on the periphery, perceived as causing so few infections as to be almost negligible in impact. A clade of monkey malaria species, primarily studied because of their potential as in vivo models for *P. falciparum* and *P. vivax*, were also known to infect Old World primates in Southeast Asia and included *Plasmodium knowlesi*, *Plasmodium cynomolgi*, and *Plasmodium inui*.

Fast forward 20 years and how things have changed! The number of global human malaria infections has dramatically declined, and there now exists a greater understanding of the importance and threat that *P. vivax* presents and acknowledgment that this species requires its own research and elimination agenda (WHO, 2015). Compelling evidence also exists that *P. ovale* is in fact two species, *P. ovale curtisi* and *P. ovale wallikeri* (Sutherland et al., 2010), morphologically similar and inhabiting sympatric ranges but genetically distinct. And most astonishing of all has been an evaluation of the zoonotic (host-switching) potential of *Plasmodium* species, due to pioneering work by Balbir Singh and colleagues identifying *P. knowlesi* as a species causing a heavy burden of clinical infections in Malaysia (Singh et al., 2004) and several