Scar tactics for immunity

Although variola major (smallpox) was eradicated by vaccination with the related orthopoxvirus vaccinia virus (VACV) via skin scarification (s.s.), researchers have begun to investigate the feasibility of renewed immunization strategies because of bioterrorism concerns. Liu and colleagues recently found that immunization via s.s. was required for the generation of superior protective immune responses to this virus. Indeed, the T-cell memory generated by recombinant VACV s.s. immunization is necessary and sufficient for protection against cutaneous challenge with the virus. In addition, lethal respiratory challenge required VACV-specific mucosal effector memory cells as well as central memory T cells. These T cells were sufficient for protection even in the complete absence of an antibody response. Furthermore, nonreplicative modified vaccinia Ankara virus—a clinically safer virus for vaccine purposes—also yielded protection when administered via s.s. as compared with delivery via intramuscular injection. Thus, these results suggest a new method for the development of safe and effective VACV immunization protocols. (Nat Med 16:224–7, 2010)

Dangers of transcription

UV radiation induces photolesions that block both DNA replication and transcription. Transcription of a gene increases its mutability by UV radiation in mouse embryonic stem cells. To examine the mechanism for transcription-associated mutagenesis (TAM), Hendriks and colleagues disrupted the Xpa gene, which is involved in global genome and transcription-coupled nucleotide excision repair (NER), and examined the impact of photolesions on the genome. In this system, UV lesions were more mutagenic upon transcription of the damaged template. In addition, these data revealed that NER protects transcribed genes from TAM. In particular, transcription enhanced cytosine deamination at UV photolesions, and this transcription-associated deamination of cytosines proved to be a critical intermediate in UV mutagenesis. This novel mechanism for UV radiation–induced mutagenesis offers an explanation for the role of transcription machinery in DNA damage sensing and provides insight into the molecular basis of UV radiation–induced carcinogenesis. (Curr Biol 20:170–5, 2010)

Cytokine targets in candidiasis

Chronic mucocutaneous candidiasis (CMC) often occurs in immunodeficiencies, e.g., in HIV infection, and protection is thought to be mediated via T cells, particularly IL-17-producing T helper type 17 cells at epithelial surfaces. CMC is the earliest and most common sign of autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED, or autoimmune polyendocrine syndrome type I), an autosomal recessive syndrome caused by defects in the autoimmune regulator (AIRE) gene. These defects invoke autoimmune responses that cause endocrine features of this disease; however, the immunodeficiencies that underlie CMC in APECED are not understood.

In two recent companion papers, Puel and colleagues and Kisand and colleagues examined IL-17 and IL-22 responses in the sera of APECED patients in order to probe the puzzling immunodeficiencies. These researchers detected significantly reduced IL-17F and IL-22 responses in patients with CMC, which suggest that these cytokines are involved in protection against CMC. Importantly, serum autoantibodies against IL-17A, IL-17F, and/or IL-22 were found in the majority of patients harboring AIRE mutations. Furthermore, these antibodies occurred more frequently in APECED patients with CMC than in those without, imparting clinical significance to the presence of these autoantibodies. Indeed, the autoantibodies were neutralizing in functional assays. In these sera, autoantibodies to other cytokines were not detected. On the basis of these observations, autoimmunity in APECED targets not only endocrine tissues but also components of the acquired immune system—specifically, IL-17A, IL-17F, and IL-22, which are involved in protection against CMC. As a result, immunosuppressive treatments and even IL-22 replacement therapy may be novel approaches to treating CMC in the future. (J Exp Med 207:291–7, 2010; J Exp Med 207:299–308, 2010)

Under the radar: bias in systematic reviews

Outcome reporting bias occurs when a subset of the original recorded outcome variables is selected for publication on the basis of the results. To assess the impact of outcome reporting bias in randomized controlled trials on a cohort of systematic reviews, Kirkham and colleagues examined the prevalence of outcome reporting bias using a nine-point classification system for missing outcome data in an unselected cohort of 283 Cochrane systematic reviews. Outcome reporting bias was suspected for at least one randomized controlled trial in 34% of the systematic reviews examined. This value, however, is higher than the number of reviews that referenced the potential for such a bias; thus, the bias problem is clearly underrecognized. In addition, outcome reporting bias was shown to affect the treatment-effect estimate in a considerable number of Cochrane reviews, which are considered among the best sources of reliable, up-to-date health-care information. These results affirm that trials should not be excluded because of a lack of relevant outcome data, and they support disclosure of randomized controlled trials before initiation and the results of such trials after completion. (BMJ 340:c365, 2010)

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