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MURINE SUPPRESSOR T CELLS: MIRAGE OR CLOUDY REALITY?

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Recently, one of our students asked me whether I still "believe in" suppressor T cells. My first impulse was to respond with a statement to the effect that belief is a religious rather than a scientific issue; however, I realized that this rather fashionable question was meant to be taken seriously and reflects a potentially valid concern that conclusions from earlier studies (in the "premolecular era") are significantly flawed. In essence, during the last few years, genes for many of the molecules that were known to function in the immune system have been cloned and T-cell clones capable of many of the functions known for the immune system have been isolated. However, molecules mediating suppression have been evasive and cell lines capable of suppressing responses have been few and far between. Therefore, many investigators now wonder whether these cells and molecules actually exist.

The difficulties in evaluating the validity of the earlier studies are compounded by the wide variety of suppressor systems that were examined and the sometimes meager evidence advanced to demonstrate that responses were actually being suppressed. Nevertheless, there are several clear-cut systems in which suppression has been demonstrated. I am most familiar with two of these systems: the allotype suppression system studied in our laboratory and the carrier-specific suppression system studied initially by the Tada group in Japan and revived in our laboratory in the context of the epitope-specific regulation of antibody responses.

In the allotype-suppression system (Herzenberg and Herzenberg, 1974; Herzenberg, 1983; Herzenberg *et al.*, 1983), $(BALB/c \times SJL)F_1$ hybrids treated with antibodies to the paternal IgG2a allotype (Igh1b) develop a specific, chronic suppression of Igh1b allotype production. This suppression can be transferred with FACS-sorted T cells and reproducibly results in a 10- to 50-fold suppression of Igh1b production by co-transferred syngeneic spleen cells. In the carrier-specific suppression system (Tada *et al.*, 1972; Tada and Okumura, 1979; Tada and Hayakawa, 1980), mice immunized with typical protein immunogens such as KLH and CGG develop suppressor T cells that suppress *in vitro* antibody production to haptens on the protein (carrier) molecule. These suppressor cells have been shown to specifically suppress antibody production *in vitro* and to transfer suppression regularly, albeit not always, to non-irradiated hosts.

The carrier-specific suppressor cells were (are) commonly believed to sup-

press antibody production by interfering with carrier-specific help. However, our studies show that these suppressor cells and soluble factors that they produce actually act to induce an epitope-specific suppressor effector mechanism that specifically blocks antibody responses to new epitopes presented on the carrier protein (Herzenberg, 1983; Herzenberg *et al.*, 1983; 1982; Herzenberg, 1986). These findings, which showed that immunizing KLH primed animals with DNP-KLH specifically suppressed anti-DNP responses, ran contrary to the widely held notion that carrier priming augments subsequent antibody responses to haptens presented on the priming carrier. Thus, they contradicted much of the dogma of the era in which they were produced.

Since that time, a number of studies have been completed confirming and extending these findings and demonstrating their importance in practical immunology (*e.g.*, Schutze *et al.*, 1987; 1985). Paradoxically, however, this appears to have served to further erode confidence in the general concepts of suppression and regulatory T cells. Perhaps this is because we have now begun to recognize the complexity of the mechanisms that control the immune system and how difficult it is to study those mechanisms *in vitro*.

I have little doubt that regulatory T cells capable of up-regulating or down-regulating immune responses exist. The evidence on which I base this conclusion is referred to above and is summarized in several reviews that we wrote over the last few years (Herzenberg and Herzenberg, 1974; Herzenberg *et al.*, 1983; 1982; Herzenberg, 1986). It does not bear repetition or further summary in the limited space available here. Rather, I would suggest that those interested in determining whether suppressor T cells exist give serious consideration to the detailed data summarized in these articles and presented in the papers to which they refer. In essence, I believe at least these data must be explained before critics who decry the existence of suppressor T cells can be seriously credited.

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