Fattening Up Allograft Rejection

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The prevalence of obesity in many societies has reached epidemic proportions, doubling since the 1980s to greater than 600 million people worldwide.[1] It clear that obesity is an important risk factor in the development of significant diseases including cardiovascular disease and diabetes. A key aspect of obesity-driven pathology relates to the impact of obesity on the immune system. One complex outcome of obesity appears to be activation of inflammatory pathways in the brain and adipose tissue, which in turn results in loss of immune homeostasis and systemic immune activation.[2] This rise in obesity has wide spread implications for transplantation. Diabetes is a major risk factor for renal failure that is often best treated with renal transplantation; however, obese subjects are at an increased risk for delayed graft function after renal transplantation,[3] and there is increasing awareness of the negative impact obesity-driven inflammation has on transplant outcomes.[1]

In this issue, Molinero and colleagues[4] used a mouse model of diet-induced obesity (DIO) to assess how obesity would impact the alloimune response during cardiac allograft rejection. Mice were fed either a standard diet (chow) or one high in fats (DIO) for 12 weeks and then transplanted with a minor mismatched cardiac allograft. Mice that were fed the high-fat diet almost doubled their weight compared with those on a normal diet and dramatically showed a trend to faster rejection times (Figure 1). Thus, there was a clear relationship between obesity and worse transplant outcomes as has been reported for renal transplant patients.[3] To investigate this phenomenon further, in vitro T cell responses were examined after stimulation with anti-CD3 mAb in the presence or absence of antigen presenting cells from DIO or chow-fed mice, respectively. When cultured with APCs from chow-fed mice, T cells from DIO mice did appear to proliferate more strongly and produce increased levels of effector molecules IFNγ and IL-17 than T cells from chow-fed mice, suggesting that an obese environment impacted T cell sensitivity to stimulation. However, a much more marked effect was seen when T cells were activated in the presence of APCs isolated from DIO mice. In this case, DIO APCs were much more potent, eliciting T cell responses at least 50% greater with respect to elaboration of effector molecules and proliferation regardless of the source of T cells. Strikingly, the enhanced T cell response was most dramatic when both the T cell and APCs were sourced from the DIO mice.

A number of other systems were used to confirm this finding, including an in vitro mixed lymphocyte reaction approach in which chow or DIO mice were immunized with full mismatched allogeneic splenocytes; in this case, T cells from immunized DIO mice again showed greater IFNγ responses in a recall response. Thus, obesity results in heightened T cell reactivity to alloantigen. The question remains as to how the increased weight impacts the alloimmune response. Phenotypic examination of the immune compartment did not reveal gross differences in the numbers of T cells, or reveal differences in regulatory T cell populations in DIO mice. However, an increase in the expression of the costimulatory molecule CD80 on macrophages and CD11b + dendritic cells was observed, suggesting that in an obese environment, APCs may harbor an enhanced capacity to elicit T cell responses. Though these data show for the first time the impact of obesity on heart transplant outcomes, further studies are warranted to better understand the underlying immune mechanism, particularly, more information on circulating serum cytokine and chemokine profiles, as well as further phenotypic and functional analysis of dendritic cell and other APC populations. It would also be very interesting to have information on whether obesity alters the effectiveness of immunosuppression and or tolerance-inducing strategies. Another key question relates to the molecular mechanism by which increased weight impacts immune activity. Some studies show that a high-fat diet, as used by Molinero and colleagues, can result in increased TNF production by proinflammatory M1 macrophages in response to an inflammatory stimuli[5]; increased levels of cytokines during the rejection response would most likely act to boost alloimmune immune activation with resultant faster rejection times as shown here by Molinero and colleagues. It is of interest that some studies also show that increased obesity specifically activates the NF-κB2 pathway,[6,7] and NF-κB2 activity has been shown to determine the outcome of dendritic cell antigen presentation.[8] This

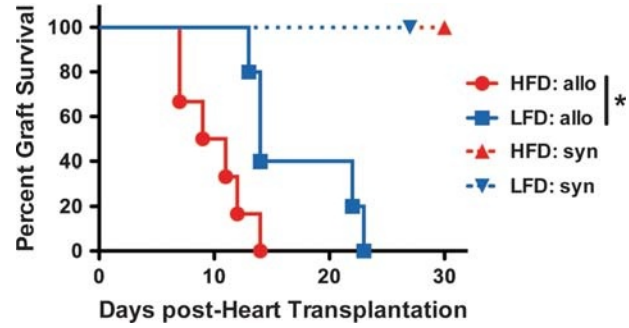

FIGURE 1. Obese mice show faster rejection of cardiac heart allografts.

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study by Molinero and colleagues clearly shows in a defined experimental system that obesity can act as a comorbidity factor leading to faster rejection and enhanced alloimmune reactivity. With as many as one third of all transplant patients for nonbariatric surgeries presenting with obesity,[1] it is critically important that we better understand the impact of obesity on immune function and transplant outcomes.

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