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Allophenic Mice: A Pillar Awaiting Its Superstructure[1]

Jeffrey L. Platt[2]

A pillar is "a firm upright support" (1) for something. A pillar may stand alone or it may support a superstructure. The article of Beatrice Mintz and Willys Silvers (2) discussed here on grafting using allophenic mice is appropriately called a pillar of immunology for which the superstructure is yet to be completed.

Mintz and Silvers posed a question long considered fundamental to immunology: What is the origin of "intrinsic" tolerance? Intrinsic tolerance refers to the natural condition of specific nonresponsiveness to self. More than 60 years before, Ehrlich and Morgenroth had reasoned that injury and atrophy of tissues might lead to the development of immune reactions against autologous cells, but the occurrence of such reactions would be "dysteleological in the highest degree" (3). To explain why autologous reactions usually do not arise, Ehrlich and Morgenroth proposed that organisms must have a *horror autotoxicus* mediated by some "regulating contrivances" and believed that studying these contrivances was "of the greatest importance" (4). If the origin of regulatory contrivances, which later would be called immunological tolerance, was important, it nonetheless evaded for decades serious and incisive investigation.

In the 1940s, Robert Owen observed that fraternal twins in cattle, which exchange hemopoietic cells through a shared placenta, have erythrocytes of both siblings in the circulation (5). Taking Owen's observation to suggest that chimerism might reflect immunological tolerance, Billingham et al. (6) found that dizygotic cattle twins, in contrast to ordinary siblings, usually would accept skin grafts from their twin. Billingham et al. (7) then demonstrated that immunological tolerance could be induced deliberately in mice by administration of large numbers of allogeneic cells. Although these observations were greeted with much enthusiasm, Mintz and Silvers questioned whether the allogeneic tolerance of cattle twins or the tolerance induced by administration of allogeneic cells to a fetus represented the "intrinsic" tolerance that all individuals exhibit to autologous cells.

To address this question, Mintz and Silvers devised an elegant model—the reconstruction of primitive embryos using primitive, genetically distinct cells—still used today. Thus, cells from early embryos with differing major histocompatibility and coat color genes were combined and implanted as hybrid embryos in pseudopregnant females. The double-sized embryos yielded newborn mice of normal size containing varying fractions of cells from each strain (e.g., some offspring had striped-, some black-, and some agouti-colored coats). These "quadraparental" mice were used as the donors and recipients of skin transplants.

Because the construction of allophenic embryos unquestionably predates any "immunological differentiation" (2), Mintz and Silvers reasoned that the immune system of allophenic mice would not be "contaminated" by immune cells from siblings to any extent more than ordinary siblings and tolerance, or lack thereof, would be truly intrinsic to the allophenic immune system. To test this concept, grafts of skin from mice of parental strains were placed on allophenic mice. Skin from parental strains was always accepted by allophenic mice of two colors. Thus, tolerance in two-color allophenic mice did represent in some manner the natural state of tolerance to self that had been noted for 60 years.

However, some results were explained less easily and indeed might be viewed as a starting point for lines of investigation today. Thus, Mintz and Silvers also found that grafts from agouti mice to black allophenic mice and grafts from black mice to agouti allophenic mice were often rejected. Rejection of black or agouti skin by allophenic mice of opposite color could reflect a lack of mosaicism or the presence of cells of one strain in numbers below some critical threshold. Since, in at least some cases, allophenic mice of one color are nonetheless mosaic (8), the rejection of skin of the opposite color by allophenic mice probably demonstrates that intrinsic tolerance requires the presence of a sufficient number or type of tolerizing cells in the host. Consistent with this concept, Billingham et al. (7) and others (9) found that introducing some large number of allogeneic cells into a fetus can induce allospecific tolerance, and yet the exchange of smaller numbers of cells between mothers and fetuses, as happens naturally in mammalian pregnancy (10–12), does not induce tolerance even though the exchanged cells can persist for years (11, 13). Exactly what determines whether the exchange of cells induces tolerance, neglect, or alloimmunity is still unknown. The allophenic mouse might still be used to advantage to address this question.

Mintz and Silvers also transplanted skin from allophenic mice to mice of parental strains, and these transplants provide seminal clues about how transplants are rejected. One such clue can be drawn from the fraction of a graft of two-color skin destroyed shortly after transplantation. This fraction corresponded roughly to the fractional representation of the allogeneic skin in the graft. Whether the impact of dosage, as such, reflects one or more of the kinetics of sensitization, the effector limb mediating injury or healing (14) is still unknown.

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More provocative than the fraction of skin rejected is the pattern of rejection. This pattern might address a question of long standing—whether the rejection of allografts is owed more to the action of CTLs or cytokine-secreting T cells. Mintz and Silvers observed "patches" of necrotic skin intermingled with healthy skin (2). This pattern suggests that allospecific cytotoxic cells rather than nonspecific effector mechanisms, such as the action of cytokines, destroy allogeneic patches. Consistent with this concept, Sutton et al. (15), studying grafts consisting of admixed allogeneic and syngeneic islets of Langerhans, observed that the allogeneic islets were destroyed whereas syngeneic islets, even those adjacent to allogeneic islets, survived. However, neither of these seminal studies provides a fully satisfying answer. Since skin grafts and islet grafts are vascularized mainly by in-growth of blood vessels of the host and rejection first appears histologically as a perivascular collection of lymphocytes (16, 17), one might have greater difficulty imagining how immune recognition connects with tissue injury. The destruction of patches of allogeneic skin and individual allogeneic islets could be owed to selective targeting of capillaries invading the graft cross-presenting allogeneic peptides. Alternatively, it might be owed to greater sensitivity of newly fashioned capillaries to cytokines or other factors produced near the graft.

Thus, in understanding the mechanism of tolerance of self and of rejection of allografts, the allophenic mouse of Mintz and Silvers provides seminal insights. Nevertheless, these insights are best considered a platform (or pillar) from which further exploration might be launched.

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