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EDITORIAL REVIEW

Regeneration of autotransplanted splenic fragments: basic immunological and clinical relevance

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In the article by Leemans *et al*. published in this issue (see pp 596–604), the antibody titres against a 23-valent pneumococcal vaccine are documented in splenectomized, spleen-autotransplanted and sham-operated rats [1]. Three days after vaccination the antibody titres against several pneumococcal antigens were increased in spleen-transplanted animals to the same extent as in control animals and significantly better than in splenectomized rats. Thus, the regenerated splenic tissue resulted in improved humoral immune reactions to a clinically relevant bacterial vaccine. Why are these data of clinical relevance?

For a long time the spleen was regarded as a superfluous organ which could be removed without side-effects, and which was excised even after minor laceration of the splenic capsule. It was estimated that about 20 years ago approx. 10 000 healthy spleens were removed per year in Germany after external or incidental trauma (e.g. during surgery of the stomach or colon). It took several decades for the increased risk of overwhelming post-splenectomy infection (OPSI) to be generally accepted, although King & Shumacker [2] had described this syndrome nearly 50 years ago. The OPSI syndrome is characterized by a high risk of mortality, especially in children, despite modern intensive care (for review see [3,4]). The most frequent reason for this sepsis are pneumococci, which are taken to be a typical T cell independent-type 2 antigen. An adequate antibody response to these bacteria depends on a functional marginal zone of the spleen [5]. This compartment is not well developed before the age of 3 years in children, which might be the reason for the higher frequency of OPSI in young children [6]. The critical role of B cells in the marginal zone for the response to TI-2 antigen has recently been summarized [7]. However, major species differences in the structure of the different splenic compartments and the localization of lymphocyte subsets have to be considered [8] when results in experimental animals on the regeneration of splenic tissue are extrapolated to the situation in humans. The implications of the regionalization of splenic lymphocyte subsets for the immune function of the spleen have also been outlined [9]. In respect to lymphocyte recirculation about 10 times more lymphocytes leave the blood in the spleen than via the high endothelial venules in lymph nodes [10]. Thus, the spleen plays a central role in many immune reactions, in particular when the microorganisms or antigen enter the blood directly, and therefore preservation of splenic tissue should be the central aim in all cases of splenic trauma.

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Meanwhile, in several original reports and reviews alternatives to splenectomy have been summarized [11,12], and special criteria outlined for the management of splenic trauma in children [13]: due to the segmental splenic blood supply partial splenectomies can be performed, lacerations of the spleen can be repaired by different techniques such as laser coagulation, application of topical haemostatic agents, or capsular sutures, and finally many patients can be conservatively treated by careful clinical observations. Based on a critical decision analysis some groups have identified important variables, such as the probability of missed injuries and non-therapeutic laparotomy deaths, and clarified the risks of OPSI and transfusion-related deaths [12,13].

How can fatal post-splenectomy sepsis be prevented? The recent critical guidelines for precautions can be recommended for details [14]. The main aspect is that the doctor and the patient have to be aware of the critical situation after splenectomy in respect to malaria infections [15], and not only of a post-splenectomy sepsis due to pneumococci but also *Haemophilus influenzae* [16] and *Neisseria meningitidis*. Therefore these patients should be vaccinated. Furthermore, lifelong prophylactic antibiotics have been recommended, especially in the first 2 years after splenectomy [14]. Finally, the patient should carry a medical card recording the splenectomy.

Why is autotransplantation of splenic tissue of interest? Particles or slices of splenic tissue regenerate when they are placed in a pouch of the greater omentum. Thus, this technique has been advocated when splenic repair is impossible. Extensive experimental animal studies have been performed on the size and total mass of the implanted splenic tissue, the phases of splenic regeneration, the site of implantation, and the restoration of splenic compartments (reviewed in [17]). There is a sequence of different phases until the splenic structure is renewed, but in most studies scars are found and the age-related splenic mass is mostly far below the normal amount. An important aspect is that obviously the age of the animal is of major importance in respect to the restored structure, the regenerated splenic mass and in particular its function, e.g. the blood flow and clearance function of bacteria [17]. Recently it was demonstrated that nerves reinnervating the autotransplants also regenerate in an age-dependent manner [18], the regeneration of stromal elements are critical [19] and, in contrast to previous concepts, some lymphocytes also survive the avascular, mostly necrotic phase before regeneration starts [20]. Future experiments should focus on the role of cytokines and chemokines in the phases of reconstruction of the autotransplanted splenic tissue, as it is now known that such factors are essential for normal structure and function of the spleen (e.g. [21,22]).

Furthermore, the functional and protective capacity of regenerated splenic tissue in humans has to be studied in more detail, as the mere presence of splenic tissue should not be taken as a guarantee of protection [23,24]. The function of regenerated splenic tissue in humans has been documented in some series collected after a number of years in different groups [25–27] and partially summarized from the literature [23,28]. For ethical reasons more detailed sequential functional studies can hardly be performed in patients.

All these data can be summarized as follows: the function of all compartments of the spleen—red pulp, marginal zone and white pulp—can be restored to a certain extent after autotransplantation of splenic tissue, but neither the clearance function nor immune reactions return to normal. There is a tendency for regeneration to be more complete in children than in adults. However, to understand the regulation of this regeneration and the mechanisms of restoring the cellular and humoral immunity, many more experiments are needed. A further unexplained observation is a functional hyposplenism in many different gastrointestinal diseases of which clinicians should be aware (reviewed in [29]). Therefore, many more detailed experiments such as those of Leemans *et al*. [1] are needed. Until these basic problems are solved every effort should be made in the clinical situation to preserve splenic tissue *in situ* and to encourage clinicians in multicentre co-operations to pool all data on the structure and function of preserved or regenerated splenic tissue to come finally to a meaningful conclusion based on a sufficiently large number of patients.

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