Inflammatory response, immunosuppression, and cancer recurrence after perioperative blood transfusion

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Editor:

We read with interest the paper of Cata and colleagues concerning perioperative blood transfusions, inflammatory response, and immunosuppression. In this interesting review, the authors discuss the understanding of the mechanisms by which transfusion affects immune function and could affect cancer progression. The authors conclude that transfusion of allogenic blood causes substantial alterations to the anti-/pro-inflammatory milieu in the recipient that seems to be proportional to the stored age of the blood products. It seems that biological factors included in these packed red blood cells that affect the innate immune function, rather than leucocytes or soluble fractions, may be responsible for tumour-promoting effects.

Arginase has gained importance due to the fact that NO synthases are dependent on the availability of L-arginine in the extracelullar environment. L-arginine is metabolized by NO synthase (NOS) to produce nitric oxide (NO) or by arginase to produce urea and ornithine, which is a precursor of polyamines, which are important during cellular proliferation. Expression of NOSs and arginases could co-regulate each other. Depletion of L-arginine by macrophages has been postulated as one of the several mechanisms that causes a decrease in CD3-zeta chain expression in cancer. In a tumour microenvironment, macrophages deplete arginine via their high arginase activity and profoundly down-regulate the tumour-infiltrating T-cells. L-arginine deficiency caused by high arginase activity, both at the tumour site and in circulating blood, has been associated not only with sustained tumour growth via polyamine synthesis but also with tumour escape from immune response. Although arginase has a short half-life of only a few hours in human blood, it might act in early stages of immunosuppression. High levels of free arginase after blood transfusion could underlie many of the deleterious outcomes, including immunosuppression and infection-related processes associated with transfusion of blood stored for long periods.

The proposed detrimental effects of prolonged blood storage have been attributed in part to haemolysis of packed erythrocytes stored for a prolonged period, which leads to an increased oxyhaemoglobin concentration and NO scavenging. Indeed, the haemoglobin level in the storage bag supernatant was found to be higher after 40 days of storage than after 3 days of storage, indicating increased haemolysis, and infusion of 40-day packed erythrocytes was recently suggested to lead to increased NO production from endothelial NOS, as a compensatory mechanism for reduced NO bioavailability caused by plasma oxyhaemoglobin scavenging of NO. However, although leucoreduced units of packed red blood cells contain fewer than 5×10^{-6} white blood cells, it should be noted that neutrophils, which undergo spontaneous cell death, constitutively express large amounts of arginase and even small contamination of packed red cell bags by neutrophils might, therefore, produce significant levels of arginase activity, apart from that derived from the red cells themselves. Recently, we found raised levels of free arginase in blood stored for long periods, which could corroborate these arguments and have implications for patients in whom immunosuppression is a major challenge.

Thus, we suggest that increased haemolysis might be an important aspect in blood transfusion, leading to elevated levels of arginase and NOS, and, thereby, to L-arginine depletion that could eventually affect immune function and cancer progression.