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Review

The aging human recipient of transfusion products

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ABSTRACT

In this review the different mechanisms of aging and frailty such as DNA defects due to impaired DNA repair, inflammatory processes, disturbances of oxidative phosphorylation are discussed together with mechanisms of cell repair. Components of blood plasma, such as the growth-differentiation protein GDF11, were shown to enhance neurogenesis and to improve the vasculature in the animal cortex and to rejuvenate muscle tissue. Advances in laboratory assays allow to identify plasma proteins that may affect tissue regeneration. This new knowledge from animal research might affect transfusion practice in geriatric patients in the future. Provided it can be translated and confirmed in human research, blood products might no longer be considered only as oxygen carriers or drugs to improve hemostasis.

In the present time blood transfusion (RBCs, plasma or platelets) should be directed by differentiated guidelines considering not only cut-off values of hemoglobin, platelet count or coagulation but also old age-specific biologic variation, comorbidities and the clinical context e.g. of bleeding.

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1. Introduction

Relevant physiologic variations in senescent organisms are known for a long time [1]. The term 'senescence' is not only used to designate the decline of age-specific fecundity but it also means longevity and life extension. In the

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context of present achievements in analytical laboratory techniques the understanding of biologic variations in life-expectancy and physiologic constitution of individuals need an update. In single cases, cellular and humoral values of innate and acquired immune system plasma proteins measured in routine clinical laboratory assays show deviations from what one might consider as normal [2–5]. With the ongoing extension of life expectancy, and the growing number of centenarians, research efforts are directed to explore the medical significance of these changes for the healthy elderly and for geriatric care. Aging is seen as a risk factor for chronic conditions limiting survival, independence and well-being – no way of evading the fate that closes on time passing by. Non microbial inflammation, apologetically termed 'inflammaging' leads to elevated IL-6, TNFα and immune chemokines, vulnerability to stress, muscle wasting and fat tissue loss. The present contribution discusses biology of aging as a possible modifier of transfusion practice. Introduced in the early 1990s, comprehensive geriatric assessment (CAG) is more and more considered a part of good medical practice (GMP) although most meta-analytic studies scrutinizing transfusion therapy in geriatrics did not use it [6]. The decision to prescribe blood products in the geriatric population should therefore not only be guided by general transfusion guidelines but is also probably better based on principles of personalized medicine. We will try to outline that prescription of blood products in geriatrics goes beyond adherence to guidelines. Perhaps more than in other disciplines principles of personalized medicine need to be considered.

2. Basic research and animal experiments

2.1. Features of the aging process might relate to transfusion-associated effects

Cellular senescence keeps track of a relatively taut signal transduction program, ending in irreversible cell cycle arrest. Experimentally, senescent growth arrest can be mimicked by different mechanisms, such as induced DNA impairment. Age related diseases in humans are at least partly caused by damages of DNA and related cell senescence. Premature aging-like (progeroid) disorders are caused by defects in DNA repair mechanisms [7]. One of them is nucleotide excision repair (NER), a pathway that operates via a "cut and patch" process: It starts with lesion recognition and proceeds to unwinding of the double helix at damaged DNA sites, lesion verification and excision and ends with gap-filling DNA synthesis.

Another lesion affects DNA inter-strand cross-links (ICLs), which may be caused not only by a variety of endogenous metabolites, environmental exposures, and cancer chemotherapeutic agents but also by senescence. In turn, senescence can also be induced by several genicidal factors, mutations, protein aggregation, increase in reactive oxygen species (ROS) as much as telomere shortening.

Animal experiments in molecular biology of aging were originally started 40 years ago [8]. DNA impaired senescent cells display a unique phenotype, which has been termed "senescence-associated secretory phenotype" (SASP). In transfusion science the adjective 'secretory' belongs to ABO-blood type secretor status in which soluble blood group glycotypes may be found in plasma, where they compete with ABO histo-blood groups in minor ABO mismatched RBC and/or platelet transfusions [9]. In the aging context, SASP may be an important driver of chronic inflammation and functions as part of a vicious cycle of inflammation, DNA damage, and senescence.

With calorie restriction and methionine restriction (MR) diets, an anti-aging paradigm came up and it was subsequently seen that MR was also keeping T cells younger and maintains kidney function; in adenocarcinoma of the mouse prostate, MR reduces tumor growth [10]. This type of tumor has been suspected to progress after transfusion of RBC, due to their transfusion-related immunomodulation (TRIM) [11,12]. Currently, common downstream mechanisms in dietary restriction may converge in mitohormesis, a term emphasized in recent applied research protocols aiming to decelerate the aging process (metformin) [13] (http://www.energymetab.ethz.ch).

The anti-glycemic drug metformin, widely prescribed as first-line treatment of type 2 diabetes mellitus (T2DM), has lifespan-extending properties [14] but the mechanism remains unclear. Diabetic or prediabetic transfusion recipients may present with a particular biochemical readiness to receive homologous cell products [15] thereby reducing pre-transfusion HbA1c levels: when using HbA1c as a predictive value to identify people at risk for T2DM or to monitor efficacy of anti-diabetic therapy, then the mean half-life of the transfused RBC concentrates of approx. 30 days must be born in mind.

We speculate that a so far unexplained biochemical constitution of transfusion recipients may also be seen in the mitochondrial capacity of oxidative phosphorylation, an important step in a variety of reactions. Mammalian sirtuin enzymes are a family of NAD+-dependent lysine-modifying acylases that control our response to diet and exercise [16]. This may make preoperative dietary preparation of patients for elective surgery an issue. The sirtuin content is augmented in a number of tissues in response to calorie restriction:metabolic decline, cancer and neurodegeneration [17] become retarded – transfusion dependency to RBC not being explored so far. The interaction of sirtuins with hypoxia-inducible factor 1 (HIF-1α) and HIF-1α components likely prepares the patient to tolerate hypoxia (Fig. 1) [18]. It is also possible that anti-aging helper components such as antioxidant enzymes, heat shock response and anti-apoptotic proteins, e.g. neuroglobin or bcl-2 family members, which constitutively play a role in anoxia-tolerance in the long term, would protect tissues from RBC-transfusion-deprived surgical patients [19].

2.2. Regeneration

The dysfunctions of organs occur semi-systemically; different organs do not necessarily age at the same pace and some tissue types may regenerate efficiently while others are irreversibly damaged [20]. The capacity of liver tissue to regenerate is mediated by infiltration not only of stem cells but also of other blood cells such as eosinophils [21]. Research efforts go into the study of systemic rejuvenation