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Platelets and Platelet transfusions: Challenges for today and tomorrow

On the way to in vitro platelet production☆

Les plaquettes de culture : une alternative transfusionnelle ?

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Abstract

The severely decreased platelet counts (10–30.10^3 platelets/μL) frequently observed in patients undergoing chemotherapy, radiation treatment or organ transplantation are associated with life-threatening increased bleeding risks. To circumvent these risks, platelet transfusion remains the treatment of choice, despite some limitations which include a limited shelf-life, storage-related deterioration, the development of alloantibodies in recipients and the transmission of infectious diseases. A sustained demand has evolved in recent years for controlled blood products, free of infectious, inflammatory and immune risks. As a consequence, the challenge for blood centers in the near future will be to ensure an adequate supply of blood platelets, which calls for a reassessment of our transfusion models. To meet this challenge, many laboratories are now turning their research efforts towards the in vitro and customized production of blood platelets.

Keywords: In vitro cultured platelets; Clinical alternative; Transfusion; Platelet production

Résumé

Dans des situations pathologiques définies, la transfusion de plaquettes sanguines à partir de concentrés plaquettaires est indiquée de manière curative ou préventive. Ces transfusions ne sont possibles que grâce au don de sang de volontaires bénévoles et anonymes plaçant la générosité des donneurs au cœur de notre système transfusionnel. Afin d'assurer la sécurité transfusionnelle, l'établissement français du sang (EFS) se doit de fournir des produits sanguins contrôlés, indemnes de risques infectieux, immunitaires et inflammatoires. Les besoins soutenus en plaquettes sanguines, associés à la faible durée de stockage des plaquettes, conduisent fréquemment à une forte pression sur les réseaux logistiques et la production de plaquettes sanguines in vitro représente un enjeu important pour la transfusion. Pour relever ce défi, de nombreux laboratoires orientent leurs efforts de recherche vers la production de plaquettes in vitro à des fins transfusionnelles.

Mots clés : Plaquettes de culture ; Substitut transfusionnel ; Transfusion ; Production de plaquettes

1. Introduction

Blood platelets are small anucleate cells (2 to 4 μm in diameter) derived from the cytoplasmic fragmentation of their MK precursor [1]. MKs are produced in the bone marrow through a highly orchestrated process [2] (Fig. 1). Hematopoietic stem cells (HSCs) lie at the apex of this process and give rise to progenitors which progressively commit to the megakaryocytic lineage to produce immature MKs [3]. MK maturation involves an increase in DNA content (up to 64 N) through endomitosis accompanied by massive enlargement of the cytoplasm, the emergence of numerous alpha and dense granules and the development of an extensive membrane network, the demarcation membrane system (DMS) [4–6]. Terminally differentiated MKs are intimately associated with the sinusoidal endothelium of the bone marrow. Following extensive cytoskeletal remodeling, fully mature MKs extend cytoplasmic projections called

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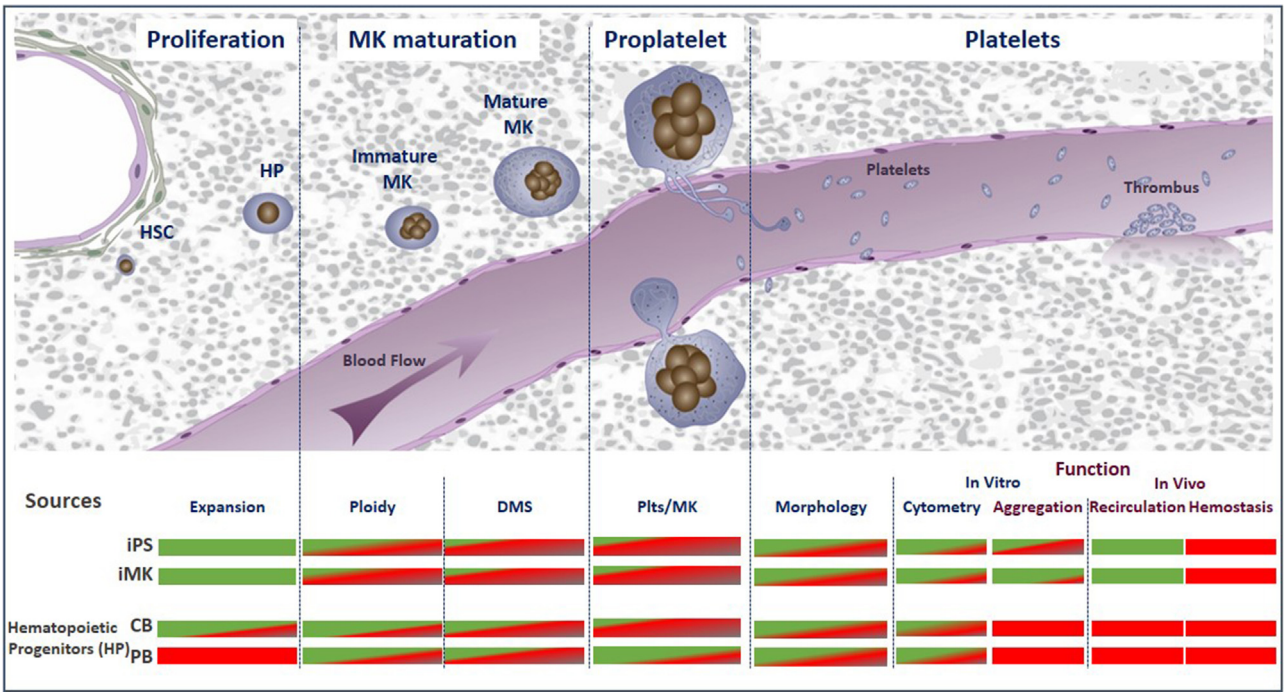

Fig. 1.

proplatelets into the vessel lumen, where platelets are released under shear forces produced by the circulating blood [7,8]. The entire sequence is strongly influenced by cytokines, extracellular matrix components, surface topography, matrix stiffness and blood flow [9]. This efficient procedure generates 10^{11} functional platelets per day to sustain an average count of 3.10^{11} platelets/L in man [10].

2. The cultured platelets in the transfusional context

More than 100 million blood donations are collected each year, but the transfusion situation varies greatly in different parts of the world. Nearly half of the donations are made in high-income countries, where less than 20% of the world's population lives (WHO). In industrialized countries, blood banks operate on a just-in-time basis. Maintaining an adequate platelet supply, ensuring their appropriate use and guaranteeing transfusion safety, together with the prevention of the transmission of infectious diseases, are the main concerns of these blood banks.

In this context, the field of platelet and transfusion research has witnessed an increasing interest in producing platelets in vitro. A number of arguments are frequently put forward to justify this research on the grounds of three main threats: i) a risk of shortage, ii) the contamination hazard and iii) the immunological risk.

2.1. The shortage threat

Maintaining appropriate stocks of platelet concentrates is becoming a major concern worldwide, due to the ever increasing number of patients experiencing long periods of severe thrombocytopenia related to bone marrow failure, anti-cancer therapy, bone marrow grafts, or immune-related or drug-induced thrombocytopenia [11]. The short in vivo half-life of human platelets imposes regular platelet transfusions for these patients, while a maximum shelf-life of 5 days further increases the demand for platelets. In the USA, platelet transfusion rose by 7.3% from 2008 to 2011 and the market for platelets is expected to grow at a rate of 5.3% per annum over the next decade [12]. This enhanced need has been cited to advocate the development of in vitro platelet production, although these figures might not apply equally to all countries. In France, for example, platelet transfusion increased by only 0.5% from 2012 to 2016 and has remained stable since, principally due to new guidelines allowing a reduction in the number of transfused platelets per unit body weight [13]. Whereas this has shelved the prospect of a short-term shortage, the long-term trend merits surveillance. In any event, all countries are facing situations with peak demands and/or periods of low blood donation (vacations, public holidays. . .) where cultured platelets could represent a real alternative to maintain optimal stocks of platelet concentrates.

2.2. The contamination hazard

Platelet transfusion has been routine practice for over five decades [14] but is however not devoid of potential risks. A bacterial contamination remains the major cause of platelet transfusion-related morbidity and mortality [15]. Fortunately, the introduction of pathogen inactivation systems and bacterial detection tests, together with careful donor screening and rigorous skin disinfection, has raised transfusion safety to levels never achieved before [16]. Nevertheless, the risks of biological hazards and contamination of blood products cannot be totally eliminated and also vary widely between countries. Platelets

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