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Platelet Genesis: Unraveling an Incredible Journey!

Platelets have a major role in preserving vascular integrity being an integral part of achieving primary hemostasis at the site of vessel injury to arrest bleeding and act as a scaffold for a stable fibrin clot.[1,2] In addition, they play a significant role in thrombosis, cancer metastasis, and inflammation. The discoid anucleate cells are derived from the polyploidy megakaryocytes (MKs) which were thought to chiefly originate from the bone marrow (BM) where platelet production takes place. MKs extend their cytoplasmic protrusions through BM sinusoids to release up to 1×10^{11} platelet daily into the blood stream to maintain a platelet count of 150–400 $\times$ 10^9/L,[3,4] once released platelets survive for ~7 days (3.4). Although MKs had been observed in the lung over eight decades ago, the contribution of lungs in platelet biogenesis was based only on indirect evidence. Howell and Donahue found that new platelets were recruited into the capillary blood in the lungs, suggesting the existence of a source of platelet production and by performing special histological staining of platelet in lung sections, they could demonstrate the presence of active giant cells involved in platelet production.[5] Other groups confirmed these findings later.[6-8]

New Insights

Earlier this year, a group of scientists from the University of California San Francisco (UCSF), refined the video microscopy technology that allowed the discovery and for the first time by direct evidence the lungs being a major site of platelet production (https://youtu.be/ZRE9 × 5XGoxA?t=51). Their astonishing findings were reported in nature.[9] The group found that the lungs produced more than half of the platelets. Furthermore, they identified a previously unknown pool of blood stem cells in the lungs capable of restoring blood cell production when the BM stem cells are depleted.[9]

This observation in mice strongly suggests that the lung may play a key role in blood formation in humans too and could lead to better understanding of platelet disorders including thrombocytopenia (reduced platelet count), a relatively common human disease. This work was made possible following the refinement of the two-photon intravital imaging technique developed by the group which allowed this extremely delicate task of visualizing the behavior of individual cells within the tiny lung vasculature of a living mouse. The engineered mouse strain platelets' emit bright green fluorescence generated from MKs in the lung vasculature which permits their tagging [Figure 1].

The new technique demonstrated MKs actively producing more than 10 million platelets per hour within the lung vasculature. This suggests that more than half of a mouse's total platelet production indeed occurs in the lung and not exclusively in the BM as previously thought for a long time. Furthermore, the video microscopy revealed the presence of MK progenitor cells and blood stem cells residing around the lung vasculature and estimated at 1 million per lung [Figure 2].

The unexpected finding of MKs and blood stem cells in the lung uncovers a fascinating stem cell trafficking network allowing free mobilization from and to the BM. To shed more light on this, the UCSF group performed a series of lung transplant experiments. First, lungs from normal donor mice were transplanted into recipient mice with fluorescent MKs, resulting in fluorescent MKs from the recipient mice turning up in the lung vasculature suggesting that the BM is the origin of platelet-producing MKs in the lung. This is a new finding. Second, lungs with fluorescent MK progenitor cells were transplanted into mutant mice with low platelet counts. A massive burst of fluorescent platelets was produced which restored the platelet count to normal over several months of observation beyond what would be anticipated for the usual lifespan of individual MKs or platelets. Third, healthy lungs in which all cells are fluorescently-tagged were transplanted into mutant mice whose BM lacked normal blood stem cells. The examination of the recipient mice BM showed that the transplanted lungs fluorescent cells soon homed into the damaged BM. They produced platelets in addition to other blood cells, including neutrophils, B and T lymphocytes supporting the premise that the mouse lungs play host to a variety of blood progenitor cells and stem cells capable of repopulating damaged BM and restoring production of several of the blood components.

This amazing work is the first description of "resident" blood progenitors in the lung. The observation of the dynamic traffic of blood stem cells and progenitors back and forth freely

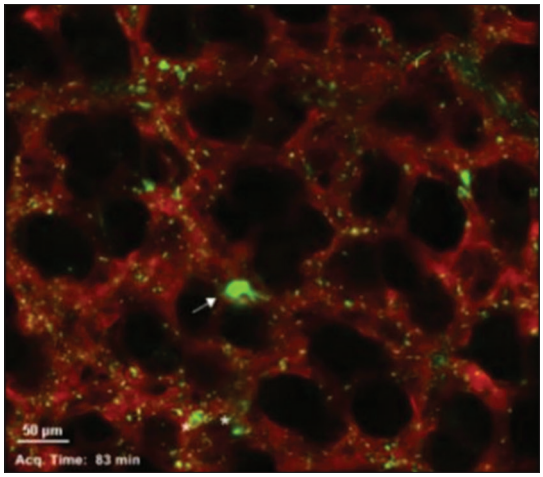

Figure 1: The release of platelets in the lung vasculature. Courtesy of University of California - San Francisco.

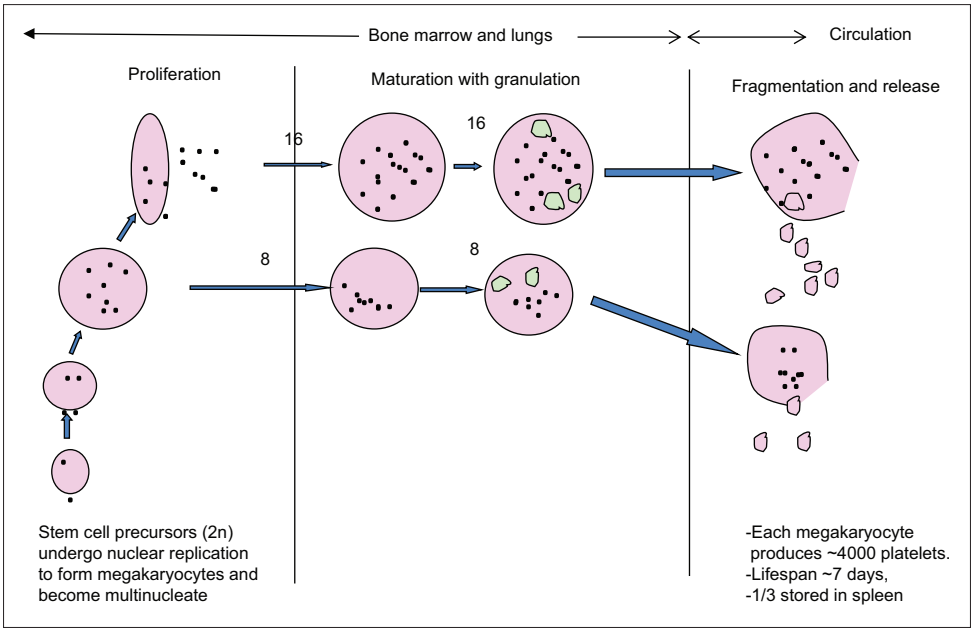

Figure 2: Current scheme of platelet production. (Courtesy of Professor David Lane, Imperial College, London).

between the lung and BM unravels platelet's birth incredible journey and opens the horizon for a new stem cell research era.

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