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The role of P2X receptors in the process of bone marrow engraftment and pharmacological mobilization of stem cells.

Summary

Purinergic signaling is considered to be an evolutionarily ancient signaling mechanism in the organism. It is a form of extracellular signaling mediated by nucleotides and nucleosides, including, most importantly, ATP. Because of ATP's established role as an intracellular energy source, the concept of purinergic signaling was initially met with strong opposition. Currently, purinergic signaling is widely accepted, and a number of studies have indicated its role in modulating homeostasis and pathological processes in the body. Purinergic signaling is a critical regulator of the nervous and cardiac system and also plays an important role in the immune response and pathogenesis of cancer.

The involvement of purinergic signaling in maintaining normal and stress-induced hematopoiesis needs reappraisal as its role is only well established for fully differentiated cells. There is a growing understanding of the role of purinergic signaling in controlling hematopoietic stem cells (HSC) used in transplantations therapies; recent evidence indicates that ATP is a vital regulator of the process of pharmacological mobilization of HSC and subsequent proper homing and engraftment of these cells into the bone marrow after hematopoietic transplantation. The engagement of the well-described purinergic receptor, P2X7, was also established.

This study aimed to explore the involvement of purinergic receptors other than P2X7 in HSC trafficking. First, the expression of all purinergic receptors on HSC of human and murine origin was evaluated. The results indicated that P2X1, P2X4, and P2X7 receptors are characterized by elevated expression on HSC when compared with mononuclear cells. Therefore, P2X1 and P2X4 receptors were selected for further studies. With the use of available experimental animal models and specific inhibitors, the role of P2X1 and P2X4 receptors in the processes determining the optimal use of HSC in hematopoietic transplantation was evaluated. Obtained results confirmed the role of the chosen receptors in pharmacological mobilization with the use of routinely utilized agents, G-CSF and AMD3100, where the inhibition of either P2X1 or P2X4 expression resulted in the defective mobilization of HSC. Subsequently, the impact of purinergic receptors in the process of proper HSC seeding after the transplantation

was evaluated. The study demonstrated that functional P2X1 and P2X4 receptors are required for optimal efficiency of the homing and engraftment processes.

The observed defective homing and engraftment also led to the prolonged time needed for complete hematological reconstitution. Finally, the obtained results indicated that ATP activates the Nlrp3 inflammasome in a P2X1 and P2X4 receptor-dependent manner, coupling purinergic signaling with innate immunity. Already published data have proven the importance of the Nlrp3 inflammasome and complement cascade, explaining their role in the trafficking of HSC.

In conclusion, obtained results shed more light on the role of purinergic signaling in the egress of HSC from the bone marrow into peripheral blood in the mobilization process and in the proper homing and engraftment of HSC into the bone marrow after transplantation. Both processes are crucial for clinical outcomes in therapies for various hematological conditions. Therefore, presented results could be utilized in unconventional clinical protocols for additional screening of patients and donors or to introduce modified protocols to ensure proper mobilization or seeding of transplanted cells.