

****This seminar will be held on FRIDAY**今回は金曜日開催します。****

●平成 26 年度医学・生命科学セミナー／D1 “Medical & Life Science Seminar, 2014”●

Role of Connexin 32 in hematopoiesis

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●Date: May 9th (**FRI**), 2014 from 17:30. ●平成 26 年 5 月 9 日 (**金**) 17:30.

●Place: Lecture Room 2, Medical Education & Library Building 3F.

●場所：医学教育図書棟 3 階 第 2 講義室



●Inviter: Prof. Takaaki Ito (Department of Pathology & Experimental Medicine)

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Since the hematopoietic system consists of a mixture of cells heterogeneous in terms of not only functionally different cellular lineages, but also different stages of differentiation, strategic analytical methods are necessary to predict the mechanisms underlying the development of hematopoietic disorders/diseases¹. In this seminar, a brief summary of topics related to hematopoiesis including that on such analytical methods will be introduced followed by the main talk on the role of connexin (Cx) 32 in hematopoiesis.

The role of gap junctions formed by connexins (Cxs) has been implicated in the homeostatic regulation of multicellular organisms, including growth control and differentiation², apoptosis³, and the synchronization of electrotonic and metabolic functions⁴. Radiation exposure and acute tissue injury induce the disconnection of Cxs, resulting in tissue damage⁵. On the other hand, the disconnection of Cxs during acute-phase cellular injury also seems to be a protective response that results in active tissue proliferation and consequent recovery⁶.

Previously, we reported the findings of our studies on the role of Cx32 expression in steady-state hematopoiesis and its potential protective role against leukemogenesis^{7,8}. Namely, in wild-type mice, Cx32 expression was solely detected in primitive hematopoietic stem/progenitor cells (HSCs/HPCs). Since Cxs are essential for multicellular organisms as mentioned above, Cxs are surmised to be present in the hematopoietic tissue to facilitate communication between HSCs/HPCs themselves rather than that between HSCs/HPCs and stromal cells. In addition, Cx32-knockout (KO) mice⁹ showed the following characteristics: first, a prominent decrease in the number of peripheral mononuclear cells (PMCs) associated with various HPCs; second, a significant increase in the number of HSCs at least until 20 weeks of age; and third, an apparently delayed regeneration of HPCs after chemical abrasion. Furthermore, the incidence of leukemogenicity induced by methylnitrosourea increased prominently.

More recently, cell kinetic analysis by continuous incorporation of bromodeoxyuridine (BrdUrd) *in vivo* in wild-type mice up to 1.5 years of age revealed the existence of a long-term stable, dormant fraction in the HPCs¹⁰. Without Cx32, the cycling fraction of HPCs apparently increased continuously at least during our observation period up to 90 days. This is consistent with the findings that the number of HPCs increased and the number of HSCs decreased simultaneously along with aging in Cx32-KO mice. In addition, the capability of bone-marrow reconstitution with HSCs by serial transplantation revealed functional impairment of primitive HSCs/HPCs derived from Cx32KO.

In summary, the above-mentioned observed findings indicate the dual functions of Cx32 in hematopoiesis; First, Cx32 function in the restoration quiescence and maintenance of primitive HSCs to prevent their exhaustion; Second, it supports HSC/HPC proliferation.

References

- 1 Hirabayashi, Y. & T. Inoue. *Chapter 24. Toxicogenomics Applied to Hematotoxicology in Handbook of Toxicogenomics* (ed J. Borlak) 583-608 (Wiley-VCH, Verlag GmbH, 2005).
- 2 Loewenstein, W.R. 1979. Junctional intercellular communication and the control of growth. *Biochim Biophys Acta* **560**: 1-65.
- 3 Wilson, M.R., T.W. Close & J.E. Trosko. 2000. Cell population dynamics (apoptosis, mitosis, and cell-cell communication) during disruption of homeostasis. *Exp Cell Res* **254**: 257-268.
- 4 Bruzzone, R., T.W. White & D.L. Paul. 1996. Connections with connexins: the molecular basis of direct intercellular signaling. *Eur J Biochem* **238**: 1-27.
- 5 Trosko, J.E., C.C. Chang & B.V. Madhukar. 1990. Modulation of intercellular communication during radiation and chemical carcinogenesis. *Radiat Res* **123**: 241-251.
- 6 Dagli, M.L., H. Yamasaki, V. Krutovskikh & Y. Omori. 2004. Delayed liver regeneration and increased susceptibility to chemical hepatocarcinogenesis in transgenic mice expressing a dominant-negative mutant of connexin32 only in the liver. *Carcinogenesis* **25**: 483-492.
- 7 Hirabayashi, Y. *et al.* 2007. Protective role of connexin 32 in steady-state hematopoiesis, regeneration state, and leukemogenesis. *Exp Biol Med (Maywood)* **232**: 700-712.
- 8 Hirabayashi, Y. *et al.* 2007. Membrane channel connexin 32 maintains Lin(-)/c-kit(+) hematopoietic progenitor cell compartment: analysis of the cell cycle. *J Membr Biol* **217**: 105-113.
- 9 Nelles, E. *et al.* 1996. Defective propagation of signals generated by sympathetic nerve stimulation in the liver of connexin32-deficient mice. *Proc Natl Acad Sci U S A* **93**: 9565-9570.
- 10 Hirabayashi, Y. & T. Inoue. 2007. Implications of hemopoietic progenitor cell kinetics and experimental leukemogenesis: Relevance to Gompertzian mortality as possible hematotoxicological endpoint. *Exp Hematol* **35**: 125-133.