Special Issue: Hematopoietic and Mesenchymal Stem Cells

Brief Review

Front runners linking inflammation and regenerative medicine

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What is the link between "Inflammation" and "Regenerative Medicine"? In this review series, we invited contributions from 5 outstanding groups of Japanese scientists. Two reviews by a distinguished group at Keio University elucidated new indicators for somatic stem cells within a bone marrow (BM) environment, with a particular focus on meschenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs), respectively. The group of Drs. Mabuchi and Matsuzaki established a new definition for mouse and human MSCs by identifying new surface markers, which also exhibit the essential properties, self-renewal activity and multi-potency, of "stem cells". MSCs show multifunctional diversity in regeneration and immunity, and have recently been strongly implicated in providing a novel "niche" for maintaining HSCs[1]. Additionally, Dr. Arai extensively described an "osteoblastic niche" for mouse HSCs, which could be different from the vascular niche or the MSC niche. This "osteoblastic niche" may display a different hierarchy, which is characterized by particular surface markers. Osteoblasts are strongly associated with bone homeostasis, whereby inflammation-dependent macrophage augmentation and differentiated osteoclasts may simultaneously be involved in the tight control of this process. It is very intriguing that a category of osteoclasts, ALCAM$^+$Sca-1$^-$ cells, highly express pluripotent stem cell markers, viz., Sox2, Oct3/4, or Nanog, which are known as Yamanaka factors; these factors are known to be involved in the maintenance and induction of pluripotent stem cells (iPS cells)[2, 3].

The group of Drs. Endo and Oike at Kumamoto University described their recent findings regarding the close association between chronic inflammation and cancer. Dr. Oike's group has previously identified angiopoietin-like protein 2 (ANGPTL2), which is produced in fat cells and which promotes chronic inflammation. They clearly demonstrate mechanisms by which ANGPTL2 promotes carcinogenesis and tumor metastasis, in which intracellular events are signaled upon binding of this protein to integrin $\alpha 5\beta 1$, also known as a fibronectin receptor. This binding leads to downstream Rac-mediated cytoskeletal reorganization and NF-κB induction, which may accelerate tumor metastasis. Of note is that the angiopoietin family (angiopoietin-1, -2, -3, and -4) were originally described as functioning within angiogenesis and HSC regulation[4, 5]; however, later, an angiopoietin-like protein family was identified as being regulators of glucose, lipid, and energy metabolism, as well as

being involved in angiogenesis. This review is therefore helpful for understanding both families of proteins and their new roles in various tissues.

Dr. Nishimura at the University of Tokyo is an expert in *in vivo* imaging technology, which enables visualization of single platelet behavior or of rolling leukocytes within vessels, including capillaries or arterioles during thrombus development or other inflammatory conditions in mouse models. Dr. Nishimura's review coherently described obesity-based chronic inflammation and related aspects of the immune system. Newly developed imaging technology, employing single- or two-photon confocal microscopy, is a powerful tool for understanding the close relationship among obesity, inflammation, and immunity.

Finally, Drs. Saito and Niwa at the Center for iPS Cell Research and Application (CiRA), Kyoto University, focused on the roles of iPS cells as a tool for elucidating pathological mechanisms in rare diseases. Disease-specific iPS cells may represent a powerful tool for replacing invaluable cellular resources that are difficult or impossible to obtain from patients, facilitating the *in vitro* recapitulation of a disease phenotype in a stepwise fashion during differentiation. Using CINCA syndrome, an autoinflammatory syndrome caused by mutations of the NLRP3 gene, as an example, they also discussed findings from previous reports of "disease-specific iPS cells". Interestingly, CINCA syndrome manifests with a severe phenotype, even though the mutation is only present in a small number of somatic cells (somatic mosaicism). Thus, Dr. Saito's group addressed the question of whether the small fraction of NLRP3-mutated cells are actually responsible for the strong auto-inflammatory response in these patients, by utilizing both normal and mutated iPS cells from a CINCA patient.

Overall, this review series exemplifies a new era in stem cell research and novel technologies, which will contribute to both research on inflammation and accomplishing regenerative medicine.

References

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