

## 骨髄由来間葉系幹細胞動員因子による非瘢痕性機能的組織再生誘導医薬開発のための基盤研究

玉井 克人 (大阪大学大学院医学系研究科)

### Development of a functional tissue regenerative therapy by a factor to recruit mesenchymal stem cells from bone marrow

Katsuto TAMAI, Osaka University

1. Tamai K, Yamazaki T, Chino T, Ishii M, Otsuru S, Kikuchi Y, Inuma S, Saga K, Nimura K, Shimbo T, Umegaki N, Katayama I, Miyazaki J, Takeda J, McGrath JA, Uitto J, Kaneda Y. (2011)

#### **PDGFR $\alpha$ -positive cells in bone marrow are mobilized by high mobility group box 1 (HMGB1) to regenerate injured epithelia.**

Proc Natl Acad Sci USA, 108: 6609-6614.

The role of bone marrow cells in repairing ectodermal tissue, such as skin epidermis, is not clear. To explore this further, this study examined a particular form of cutaneous repair, skin grafting. Grafting of full thickness wild-type mouse skin onto mice that had received a green fluorescent protein-bone marrow transplant following whole body irradiation led to an abundance of bone marrow-derived epithelial cells in follicular and interfollicular epidermis that persisted for at least 5 months. The source of the epithelial progenitors was the non-hematopoietic, platelet-derived growth factor receptor alpha-positive (Lin<sup>-</sup>/PDGFR $\alpha$ <sup>+</sup>) bone marrow cell population. Skin grafts release high mobility group box 1 (HMGB1) *in vitro* and *in vivo* which can mobilize the Lin<sup>-</sup>/PDGFR $\alpha$ <sup>+</sup> cells from bone marrow to target the engrafted skin. These data provide new insight into how skin grafts facilitate tissue repair and identify novel strategies germane to regenerative medicine for skin and perhaps other ectodermal defects or diseases.

2. Tamai K, Kaneda Y, Uitto J. (2009)

#### **Molecular therapies for heritable blistering diseases.**

Trends Mol Med, 15: 285-292.

Tremendous progress has been made over the past two decades in understanding the molecular genetics of heritable skin diseases. The paradigm for such conditions is epidermolysis bullosa (EB), which comprises a group of heritable blistering disorders caused by mutations in ten genes expressed in the cutaneous basement membrane zone and has high morbidity and mortality. Identification of distinct mutations has improved the diagnosis and subclassification of EB, leading to improvements in disease prognosis, and has provided a basis for prenatal and pre-implantation genetic diagnosis for this disorder. Nevertheless, there is no cure or effective treatment for EB. Here, we review recent exciting developments in the areas of molecular therapies, including gene therapy, protein replacement therapy and bone-marrow-derived stem cell transfer, as potential new avenues to treat EB and other currently intractable heritable skin diseases.

3. Otsuru S, Tamai K, Yamazaki T, Yoshikawa H, Kaneda Y. (2008)

#### **Circulating bone marrow-derived osteoblast progenitor cells are recruited to the bone-forming site by the CXCR4/stromal cell-derived factor-1 pathway.**

Stem Cells, 26: 223-234.

Previous studies demonstrated the existence of osteoblastic cells in circulating blood. Recently, we reported that osteoblast progenitor cells (OPCs) in circulation originated from bone marrow and contributed to the formation of ectopic bone induced by implantation of a bone morphogenetic protein (BMP)-2-containing collagen pellet in mouse muscular tissue. However, the character of circulating bone marrow-derived osteoblast progenitor cells (MOPCs) and the precise mechanisms involving the circulating MOPCs in the osteogenic processes, such as signals that recruit the circulating MOPCs to the osseous tissues, have been obscure. In this report, we demonstrated for the first time that the MOPCs were mobilized from intact bones to transiently occupy approximately 80% of the mononuclear cell population in the circulating blood by BMP-2-pellet implantation. The mobilized MOPCs in the circulation did not express the hematopoietic marker CD45 on their surface, but they expressed CD44 and CXCR4, receptors of osteopontin and stromal cell-derived factor-1 (SDF-1),

respectively. The MOPCs isolated from the mouse peripheral blood showed the ability to be osteoblasts in vitro and in vivo. Furthermore, the MOPCs in the circulation efficiently migrated to the region of bone formation by chemoattraction of SDF-1 expressed in vascular endothelial cells and the de novo osteoblasts of the region. These data may provide a novel insight into the mechanism of bone formation involving MOPCs in circulating blood, as well as perspective on the use of circulating MOPCs to accelerate bone regeneration in the future.

4. Chino T, Tamai K, Yamazaki T, Otsuru S, Kikuchi Y, Nimura K, Endo M, Nagai M, Uitto J, Kitajima Y, Kaneda Y. (2008)

**Bone marrow cell transfer into fetal circulation can ameliorate genetic skin diseases by providing fibroblasts to the skin and inducing immune tolerance.**

Am J Pathol, 173: 803-814.

Recent studies have shown that skin injury recruits bone marrow-derived fibroblasts (BMDFs) to the site of injury to accelerate tissue repair. However, whether uninjured skin can recruit BMDFs to maintain skin homeostasis remains uncertain. Here, we investigated the appearance of BMDFs in normal mouse skin after embryonic bone marrow cell transplantation (E-BMT) with green fluorescent protein-transgenic bone marrow cells (GFP-BMCs) via the vitelline vein, which traverses the uterine wall and is connected to the fetal circulation. At 12 weeks of age, mice treated with E-BMT were observed to have successful engraftment of GFP-BMCs in hematopoietic tissues accompanied by induction of immune tolerance against GFP. We then investigated BMDFs in the skin of the same mice without prior injury and found that a significant number of BMDFs, which generate matrix proteins both in vitro and in vivo, were recruited and maintained after birth. Next, we performed E-BMT in a dystrophic epidermolysis bullosa mouse model (*col7a1(-/-)*) lacking type VII collagen in the cutaneous basement membrane zone. E-BMT significantly ameliorated the severity of the dystrophic epidermolysis bullosa phenotype in neonatal mice. Type VII collagen was deposited primarily in the follicular basement membrane zone in the vicinity of the BMDFs. Thus, gene therapy using E-BMT into the fetal circulation may offer a potential treatment option to ameliorate genetic skin diseases that are characterized by fibroblast dysfunction through the introduction of immune-tolerated BMDFs.