Macrophages play a pivotal role in host defense against multiple foreign materials such as bacteria, parasites and artificial devices. Some macrophage lineage cells, namely osteoclasts and foreign body giant cells (FBGCs), form multi-nuclear giant cells by the cell–cell fusion of mono-nuclear cells. Osteoclasts are bone-resorbing cells, and are formed in the presence of RANKL on the surface of bones, while FBGCs are formed in the presence of IL-4 or IL-13 on foreign materials such as artificial joints, catheters and parasites. Recently, fusiogenic mechanisms and the molecules required for the cell–cell fusion of these macrophage lineage cells were, at least in part, clarified. Dendritic cell specific transmembrane protein (DC-STAMP) and osteoclast stimulatory transmembrane protein (OC-STAMP), both of which comprise seven transmembrane domains, are required for both osteoclast and FBGC cell–cell fusion. STAT6 was demonstrated to be required for the cell–cell fusion of FBGCs but not osteoclasts. In this review, advances in macrophage cell–cell fusion are discussed.

Macrophage Giant Cells

Multinuclear macrophage giant cells were described by Evans et al. in 1914 as giant cells associated with tuberculosis.1 Multinuclear giant cells were also observed in association with tumors and foreign materials,2,3 and their multi-nucleation was considered to be the result of the cell–cell fusion of mono-nuclear cells rather than abnormal cell division with a lack of cytokines.4 The formation of multi-nuclear giant macrophages by cell–cell fusion was experimentally proved by Aronson and Elberg in 1962.4 Osteoclast cell–cell fusion was described by Jee, Nolan, and Tonna in 1963.5,6

Macrophage Fusion and Cytokines

Macrophage giant cell formation in vitro was attempted by Galindo in 1973.7 Galindo treated normal rabbit alveolar macrophages with supernatants of Bacillus Calmette–Guerin (BCG)-sensitized lymph node cells to promote multi-nuclear macrophage formation, and stated that macrophage fusion factor (MFF) was released from sensitized T cells upon stimulation with a specific antigen.8 In 1988, McInnes and Rennick reported that multi-nuclear macrophages were formed by IL-4,9 and that MFF was likely to be IL-4.

From then, multi-nuclear giant macrophage formation has been promoted by IL-4 or other cytokines such as IL-13 and their combination, such as IL-4,9 IL-13,10 GM-CSF plus IL-4, IL-3 plus IL-4, M-CSF plus IL-4, and M-CSF + IL-13.11-13

RANKL and Osteoclastogenesis

In vitro osteoclast formation was established by a co-culture system of osteoblastic and osteoclast progenitor cells.16 Osteoclasts were formed on the osteoblastic cells in the presence of osteotropic factors such as 1,25(OH)2D3, and the direct interaction of osteoblastic and osteoclast progenitor cells was reportedly required for osteoclast formation.16 Thus, some membrane-bound factors expressed in osteoblasts were considered to be required for osteoclast formation.

Osteoclast formation was reportedly negatively regulated by osteoclastogenesis inhibitory factor (OCIF)/osteoprotegerin (OPG), a soluble receptor belonging to the TNFα receptor superfamily.17,18 Since OCIF/OPG inhibited osteoclast formation by binding to 1,25(OH)2D3-treated osteoblastic cells, the membrane-bound osteoclastogenesis inducing factor expressed in osteoblastic cells was considered to be the ligand of OCIF/OPG.19 Indeed, the cytokine, which was required for osteoclastogenesis and was identified as the OCIF/OPG binding ligand: osteoclast differentiation factor, ODF, and osteoprotegerin ligand, OPGL,20,21 was a membrane-bound ligand belonging to the TNF superfamily, and the expression was stimulated upon 1,25(OH)2D3 treatment. ODF/OPGL was now called receptor activator of nuclear factor kappa B ligand (RANKL) since ODF/OPGL was identical to RANKL, which was identified before the cloning of ODF/OPGL.22 RANKL was found to be expressed in T cells and activate dendritic cells through its receptor, RANK, expressed in dendritic cells.23 Although RANKL was a membrane-bound ligand, as expected, the soluble form of RANKL also actively induced osteoclast differentiation, and osteoclasts were formed in the presence of the soluble form of RANKL and macrophage colony stimulating factor (M-CSF), which is also an essential cytokine for osteoclastogenesis,24 without osteoblastic cells.20

Identification of DC-STAMP: An Essential Cell–Cell Fusion Regulator of Macrophages and Osteoclasts

The identification of RANKL enabled us to screen for osteoclast-specific genes since osteoclasts were formed without osteoblastic
cells. We further established a pure osteoclast culture system by culturing purified osteoclast progenitor cells in the presence of M-CSF and a soluble form of RANKL (hereafter termed RANKL).\textsuperscript{24–26} We found that osteoclast cell–cell fusion was promoted by RANKL stimulation,\textsuperscript{27} and thus, we tried to isolate osteoclast fusion molecules by subtractive screening between M-CSF + RANKL-induced multi-nuclear osteoclasts and M-CSF-induced mono-nuclear macrophages.\textsuperscript{13} We identified dendritic cell specific transmembrane protein (DC-STAMP), a seven transmembrane protein, as a highly expressed molecule in osteoclasts with this screening, and DC-STAMP was not expressed in M-CSF-treated mono-nuclear macrophages but was strongly upregulated by stimulation with RANKL.\textsuperscript{13} DC-STAMP was originally identified in dendritic cells as DC-STAMP and IL-4-stimulated macrophages as IL-4-induced (FIND), respectively.\textsuperscript{28,29} DC-STAMP was also identified in osteoclasts and implicated in osteoclast differentiation.\textsuperscript{30} We generated DC-STAMP-deficient mice, and found that they exhibited complete abrogation of multi-nuclear osteoclast formation in vivo and in vitro.\textsuperscript{13} Since tarrtrate resistance acid phosphatase (TRAP), a marker of osteoclasts, or other osteoclast differentiation markers such as Cathepsin K were equally expressed in DC-STAMP-deficient mono-nuclear osteoclasts as multi-nuclear wild-type osteoclasts, DC-STAMP was considered specifically required for osteoclast cell–cell fusion rather than differentiation.\textsuperscript{13} Osteoclast cell–cell fusion was reportedly promoted in heterogeneous osteoclast precursors expressing low and high levels of DC-STAMP.\textsuperscript{31} DC-STAMP expression in osteoclasts was promoted by nuclear factor of activated T cells 1 (NFATc1),\textsuperscript{13,32} an essential transcription factor for osteoclastogenesis.\textsuperscript{33} DC-STAMP was also demonstrated to be promoted by vitamin E-induced MITF, or tal1-PU.1/MITF pathway in osteoclasts.\textsuperscript{34,35} Similar to osteoclasts, multi-nuclear FBGC formation was also completely inhibited in DC-STAMP-deficient mice in vivo and in vitro; thus demonstrating that DC-STAMP was required for both osteoclast and FBGC cell–cell fusion.\textsuperscript{13} DC-STAMP expression in FBGCs was regulated by NFκB.\textsuperscript{13}

Identification of OC-STAMP

Since DC-STAMP was identified as specifically expressed in RANKL-induced multi-nuclear osteoclasts but not in M-CSF-induced mono-nuclear macrophages, we overexpressed DC-STAMP in M-CSF-induced macrophages and analyzed whether cell–cell fusion was induced in DC-STAMP-overexpressed macrophages without RANKL.\textsuperscript{36} However, cell–cell fusion was not induced in DC-STAMP-overexpressed macrophages without RANKL, suggesting that some molecules other than DC-STAMP were required for osteoclast cell–cell fusion.\textsuperscript{36} Then, we tried to isolate the next molecules for osteoclast cell–cell fusion, and identified osteoclast stimulatory transmembrane protein (OC-STAMP) in osteoclasts.\textsuperscript{14} Similarly to DC-STAMP, OC-STAMP was a seven transmembrane protein, and was not expressed in M-CSF-treated macrophages but was strongly upregulated with RANKL stimulation.\textsuperscript{14} We generated OC-STAMP-deficient mice, and found that they exhibited complete abrogation of osteoclast cell–cell fusion in vivo and in vitro.\textsuperscript{14} Since osteoclast differentiation marker expression in OC-STAMP-deficient mono-nuclear osteoclasts was equivalent to those with wild-type multi-nuclear osteoclasts, OC-STAMP was considered specifically required for osteoclast cell–cell fusion rather than differentiation as DC-STAMP.\textsuperscript{14} OC-STAMP was also demonstrated to be required for FBGC cell–cell fusion.\textsuperscript{14} Recently, OC-STAMP antibody was demonstrated to inhibit osteoclast and FBGC cell–cell fusion.\textsuperscript{37} Thus, DC-STAMP and OC-STAMP were both required for osteoclast and FBGC cell–cell fusion.

STATs and Macrophage Cell–Cell Fusion

Signal transducer and activator of transcription (STAT) family molecules were found to be required for the transduction of cytokine signals. STATs consist of seven family members, STAT1–4, 5A, 5B, and 6, and each STAT has its own cytokines to transduce their signals. Among them, STAT6 plays a pivotal role in transducing signals of IL-4 and IL-13, both of which promote FBGC formation.\textsuperscript{9,15} Thus, STAT6 was suggested to play a role in macrophage cell–cell fusion. Indeed, Moreno et al. reported that STAT6 was required for FBGC cell–cell fusion, and that STAT6-deficient mice showed the marked inhibition of FBGC multi-nucleation.\textsuperscript{38} They demonstrated that expressions of DC-STAMP and E-cadherin were significantly inhibited in STAT6-deficient FBGCs.\textsuperscript{38} We also found that STAT6-deficient mice exhibited significant inhibition of multi-nuclear FBGC formation in vivo and in vitro, and the expressions of DC-STAMP and OC-STAMP were both significantly inhibited in STAT6-deficient FBGCs.\textsuperscript{14} Thus, DC-STAMP and OC-STAMP were considered the targets of IL-4–STAT6 signals.\textsuperscript{15} In addition, since FBGC formation was promoted in the presence of GM-CSF plus IL-4, we searched for activated molecules under stimulation of GM-CSF, and found that STAT1 was activated by GM-CSF.\textsuperscript{15} STAT1-deficient cells showed accelerated cell–cell fusion in FBGCs, suggesting that STAT1 was considered an inhibitor of FBGC multi-nucleation.\textsuperscript{15} STAT1 and STAT6 reportedly reciprocally regulate each other in T cells.\textsuperscript{19} Interestingly, STAT1 was strongly activated in STAT6-deficient FBGCs in the presence of GM-CSF + IL-4, indicating that STAT6 was the inhibitor of STAT1 in FBGCs, and that IL-4 induced STAT6 activation followed by STAT1 suppression was required for FBGC formation (Fig. 1).\textsuperscript{15} Indeed, STAT1-deficiency was sufficient to promote cell–cell fusion in FBGCs without IL-4.\textsuperscript{15} In contrast, neither STAT1 nor STAT6 were required for osteoclast cell–cell fusion.\textsuperscript{15}

Future Perspectives Regarding JAK-STAT and Macrophage Fusion

Various factors discussed below were identified and demonstrated to play a role in cell–cell fusion of osteoclasts or macrophages or both; however, their regulation by STATs was not fully demonstrated. Since IL-4/STAT6-STAT1 signals are specifically required for macrophage cell–cell fusion and DC-STAMP/OC-STAMP expression, the other molecules required for macrophage cell–cell fusion are likely to be regulated by STAT6-STAT1.
STAT6 is activated by IL-4 and IL-13, both of which promote macrophage fusion, via JAK1 and JAK3.40 Meanwhile, STAT1 is activated by interferon gamma via JAK1 and JAK2.40 JAK1-deficient mice exhibited impaired lymphoid development,41 while JAK2-deficient mice presented with no definitive erythropoiesis.52-54 JAK3-deficient mice exhibited defective lymphoid development and dysregulated myelopoiesis.44,46 However, the roles of JAKs in macrophage fusion were not demonstrated. The molecules demonstrated to play a role in osteoclast or macrophage cell–cell fusion are listed in Tables 1, 2, and 3. It is still possible that other STATs contribute to osteoclast and macrophage cell–cell fusion, and further studies will uncover the molecular mechanisms of osteoclast and macrophage cell–cell fusion by STATs.

Molecules for both osteoclast and macrophage cell–cell fusion. Meltrin-α, also called A disintegrin and metalloprotease 12 (ADAM12), was demonstrated to play a role in both osteoclast and macrophage cell–cell fusion by using anti-sense oligo.47 The d2 isoform of vacuolar (H[+]i) ATPase (v-ATPase) V(0) domain (Atp6v0d2) was demonstrated to play a role in cell–cell fusion of both osteoclasts and FBGCs, and Atp6v0d2-deficient cells showed marked inhibition of osteoclast and FBGC cell–cell fusion.48 Monocyte chemoattractant protein 1 (MCPI, also called chemokine C–C motif ligand 2, CCL2) and its receptor chemokine C–C motif receptor 2 (CCR2) were implicated in macrophage and osteoclast–cell fusion.49 Meanwhile, MCPI/CCR2 was demonstrated to play a role in osteoclast differentiation rather than cell–cell fusion.50-52 ADAM8 was reportedly highly expressed in osteoclasts, and overexpression of ADAM8 in transgenic mice under a control of TRAP-promoter resulted in increased multi-nucleation of osteoclasts and bone loss.53

Molecules for osteoclast cell–cell fusion. E-cadherin, intercellular adhesion molecule-1 (ITAM1), and leukocyte function-associated antigen-1 (LFA1) were demonstrated to be involved in osteoclast–cell fusion and maturation by using a neutralizing antibody.53-56 CD200-deficient mice exhibited inhibition of osteoclast–cell fusion and an increased bone mass.57 SH3 and PX domains 2A (SH3PXD2A, also called Tks5), a substrate of c-Src, was demonstrated to play a role in osteoclast–cell fusion downstream of phosphoinositide 3-kinase and Src.58

Molecules for macrophage cell–cell fusion. Interferon-gamma (IFNγ) and intercellular adhesion molecule-1 (ICAM1) were reportedly involved in macrophage cell–cell fusion, and monoclonal antibodies against LFA1 or ICAM-1 inhibited the multi-nuclear macrophage formation.59 Macrophage fusion receptor (MFR: also called SHPS-1), belonging to the immunoglobulin (Ig) superfamily, was highly expressed in macrophages at the stage of cell–cell fusion, and monoclonal antibodies against MFR or the soluble form of the extracellular domain of MFR blocked the cell–cell fusion of macrophages.60,61 CD47 is a ligand of MFR, and it was also implicated in macrophage–cell fusion.62 DNA-Y activating protein of 12 kD (DAP12), DAP12 associated receptor triggering receptor expressed by myeloid cells 2 (TREM2), and the downstream signaling molecule Syk were shown to be required for IL-4-induced macrophage cell–cell fusion by using DAP12-knockin and knockout mice, Syk-knockout mice and RNAi against DAP12 and TREM2.63 Matrix metalloprotease 9 (MMP9) and scavenger receptor CD36 were shown to play a role in macrophage cell–cell fusion by using their blocking antibodies and MMP9- or CD36-deficient mice.64,65 Rac inhibitor NSC23766 or Rac1 knockdown by siRNA resulted in attenuation of macrophage cell–cell fusion.66

Disclosure of Potential Conflict of Interest
No potential conflicts of interest were disclosed.

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Table 1. Putative regulators for both osteoclast and macrophage cell–cell fusion

| Molecule       | Osteoclast fusion | Macrophage fusion | Materials used | References |
|----------------|-------------------|-------------------|----------------|------------|
| DC-STAMP       | Complete inhibition | Complete inhibition | DC-STAMP KO | 13         |
| OC-STAMP       | Complete inhibition | Complete inhibition | OC-STAMP KO | 14         |
| Meltin α (ADAM12) | 70% inhibition | 50% inhibition | Anti-sense oligo | 34         |
| Atp6v0d2       | Defective         | Severely impaired | Atp6v0d2 KO | 35         |

Table 2. Putative regulators for both osteoclast cell–cell fusion

| Molecule       | Osteoclast fusion | Materials used | References |
|----------------|-------------------|----------------|------------|
| CD200          | Reduced           | Soluble protein of extracellular domain of CD200R | 43         |
| SH3PXD2A (Tks5) | Impaired         | siRNA for Tks5 | 44         |

Table 3. Putative regulators for both osteoclast and macrophage cell–cell fusion

| Molecule       | Macrophage fusion | Materials used | References |
|----------------|-------------------|----------------|------------|
| MCP1 (CCL2)   | Reduction         | CCL2 KO        | 36         |
| LFA1          | Inhibited (IFN-γ induced macrophage fusion) | Monoclonal Ab against LFA1 | 45         |
| ICAM1         | Inhibited (IFN-γ induced macrophage fusion) | Monoclonal Ab against ICAM1 | 45         |
| MFR (SHPS1)   | Inhibit           | Monoclonal Ab against MFR | 46         |
| CD47          | Prevent           | Extracellular domain of MFR | 47         |
| DAP12         | Impaired          | DAP12 | 49         |
| TREM2         | Severe impaired   | TREAM2 siRNA   | 49         |
| Syk           | Reduced           | Syk KO         | 49         |
| MMP9          | Reduced           | Function-blocking Ab | 50         |
| CD36          | Severely impaired | CD36 KO        | 51         |
| Rac1          | Attenuated        | Inhibitor of Rac activation (NSC23766) | 52         |

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