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EGFR signaling drives multipotential stromal cells to produce multiple growth factors and cytokines via early growth response gene-1

Kenichi (Ken) Tamama University of Pittsburgh School of Medicine, USA Cell therapy with adult bone marrow multipotential stromal cells / mesenchymal stem cells (MSCs) presents a promising approach to promote wound healing and tissue regeneration. The strong paracrine capability of various growth factors / cytokines (GFs/CKs) is a key mechanism of MSC-mediated wound healing and tissue regeneration, and the goal of this study is to understand the underlying mechanism that supports the strong paracrine machineries in MSCs. Our previous studies showed that EGF treatment induced GF production in MSC *in vitro*, and we hypothesize that *EGFR signaling plays a pivotal role in MSC paracrine activity*. MSC treatment with EGF up-regulated the gene expression of GFs/CKs including HB-EGF, PDGFA, VEGFA, LIF, IL-11. Database analyses revealed that the promoter regions of these genes contain the binding sequences of early growth response gene 1-3 (Egr 1-3). EGF strongly induced the gene expression of Egr 1-3, HB-EGF, and EGFR, which was reversed by PKC inhibitor bisindolylmaleimide I BIM. Gene knockdown of Egr1 reduced the expression of many of the GFs/CKs that had been up-regulated by EGF. MSC treatment with PDGF-BB, HGF, or G-CSF also up-regulated the gene expression of HB-EGF.

In summary, EGFR signaling up-regulates multiple GFs/CKs, including its own ligand HB-EGF, through a signaling pathway most likely mediated by PKC and Egr-1. These data suggest the possible presence of autocrine signaling with EGFR ligands, which would enhance MSC production of the GFs/CKs.

## Biography

Dr. Tamama received both his M.D., and Ph.D. from Gunma University in Japan. He finished clinical pathology (laboratory medicine) residency training and post-doctoral research fellowship at the University of Pittsburgh. As a board-certified clinical pathologist, he oversees a toxicology laboratory at the University of Pittsburgh Medical Center. He has been studying MSC biology since 2002, when he joined a research laboratory of Dr. Alan Wells as a trainee at the University of Pittsburgh. He has published more than 20 articles in reputed journals and books.