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Study on interaction between cancer cells and mesenchymal stem cells via indirect or direct cell-to-cell connection

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Mesenchymal stem cells (MSCs), identified as a bone marrow-derived cell population, display self-renewal ability and can also differentiate into mesodermal lineages such as cartilage, adipose, connective tissue, and tendon. Recently, increasing evidence shows that MSCs could localize to the site of tumorigenesis and has important effects on cancer cells by providing cancer cells with essential microenvironment, but the relationship between stem cells and tumor cells and the mechanisms underlined are not clear. In the present study, we have examined the interaction between human cancer cells (HepG2 and Hela) and human MSCs (hMSCs) by the addition of conditioned medium obtained from coculture or by transwell culture (using a filter as an insert). For establishing direct cell-to-cell cocultivation, we have developed a nanoparticle-based differential labeling approach using internalizing quantum dots (i-QDs), which is a noninvasive and nondisruptive way to monitor and distinguish the co-cultured cells spatio-temporally. We demonstrate that tumor cells display decreased cell proliferation and increased cell death in dose-dependent manner as assessed by CCK-8 or DNA content assay. The growth-inhibitory effect is further confirmed by performing cell cycle assay showing that cell cycle is arrested in the G^2/M transition and the cell apoptotic rate exhibited higher level as compared to that without the presence of hMSCs. Furthermore, we show that labeled hMSCs traffic from bone marrow migrate towards cancer cells for interaction under fluorescence microscope at different time points. This suggests that hMSCs, when co-cultured with cancer cells, interact with cancer cells and have important effect on the tumor cells growth. Additionally, we test whether the mitogen-activated protein kinase kinase (PI3K) and mitogen-activated protein kinase pathways, which play an important role in cell proliferation, differentiation, and tumorigenesis, are involved in hMSC-mediated regulation, and find that protein kinase B (PKB), phosphorylated PKB (P-PKB), and extracellular signal-regulated kinases (ERK1/2) etc; key components of PI3K or MAPK pathway, significantly decreased in the expressions as shown by using real-time quantitative reverse transcription polymerase chain reaction (QRT-PCR) and western blotting analysis. Thus it could be concluded from the results that hMSCs interact with cancer cells by providing them with microenvironment to regulate the tumor survival and growth, and the PI3K/MAPK signaling pathway activation is required for the induction of suppression of tumorigenesis by hMSCs. This would extend our understanding of the correlation between human MSCs and cancer cells, which might be important in developing novel interfering strategies for improved tumor therapy and drug discovery.

Biography

Xiaohui Long has Ph.D in Biochemistry and Molecular Biology (2006). She is a staff senior researcher at the National Institute of Advanced Industrial Science and Technology (AIST), Japan. Her research group is currently working on the development of new labeling techniques for *in vitro* and *in vivo* tracking of cells and the application of new labelings' for screening the interaction between cancer cells and mesenchymal stem cells using fluorescence microscope. She has 1 patent, published over 30 papers in Biology and Biochemistry journals, and serving as an member of *National Chemistry Association*.