Calcium efflux pump, PMCA2, in human breast tissue with lactational change and as a therapeutic target in breast cancer

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Abstract

Calcium pumps and channels modulate cell proliferation and apoptosis by regulating intracellular calcium (Ca2+). The plasma membrane Ca2+ ATPase isoform, PMCA2, is a calcium efflux mechanism that extrudes Ca2+ from the cytosol into the extracellular space. PMCA2 has a restricted expression, including expression in cochlear hair cells and cerebellar Purkinje cells. PMCA2 expression is increased in mouse mammary glands during lactation where it plays a major role in the excretion of Ca2+ into milk; however, PMCA2 expression has not been assessed in human breast tissue exhibiting lactational changes. Our previous studies have shown that PMCA2 mRNA levels are elevated in some breast cancer cell lines and that pan-PMCA antisense attenuates the proliferation of MCF-7 breast cancer cells. However, the consequences of silencing PMCA2 in breast cancer cells are still not well understood. Our study assessed PMCA2 expression in breast tissue exhibiting lactational change and in human malignant breast tissue samples. The role of PMCA2 in the proliferation of breast cancer cells was also evaluated. Immunohistochemistry using a rabbit anti-PMCA2 antibody showed membranous PMCA2 expression in the luminal epithelium of breast tissue exhibiting lactational change. PMCA2 expression was assessed in human breast tumor samples assembled into tissue microarrays. Nine of 96 breast tumours (9.4%) showed membranous PMCA2 staining. PMCA2 expression did not significantly correlate with the breast cancer pathological markers, estrogen, progesterone or HER2 receptor status. High-content imaging demonstrated that PMCA2 silencing in MDA-MB-231 breast cancer cells is associated with a reduction in cell number and an inhibition of the percentage of S-phase positive cells. The effect of PMCA2 silencing combined with various cytotoxics (cisplatin, doxorubicin or mitomycin C) on cell proliferation was assessed in MDA-MB-231 cells using a kinetic imaging system (IncuCyte). The results showed that PMCA2 silencing promotes the effects of some cytotoxics. These findings indicate that PMCA2 protein expression is elevated during human lactation and in some breast cancers. Inhibitors of PMCA2 may represent a novel therapeutic strategy for some breast cancers.

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Antibody-based targeting of TNF-ligands for cancer therapy

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Abstract

The tumor necrosis factor (TNF) ligand and cognate TNF receptor superfamily constitute an important immunoregulatory axis pivotal for the correct execution of immune responses. TNF ligand and receptor family members among others are involved in induction of cell death in malignant cells as well as in providing co-stimulatory signals that help mount effective anti-cancer immune responses. This diverse and important regulatory role in immunity has sparked great interest in the development of TNFL/TNFR-targeted cancer immunotherapeutics. Here, I will discuss our cancer immunotherapeutic drug discovery and development program using selected examples of the TNF-ligand superfamily.

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Effect of repeated passaging and cell density on proliferation and differentiation potential of cord blood unrestricted somatic stem cells

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Abstract

The ease of culture expansion of unrestricted somatic stem cells (USSCs) represents one of their primary advantages in clinical strategies. However, genetic alterations during culture expansion undoubtedly affect their therapeutic potential. Telomere shortening with aging is another factor that leads to aberrant stem cell functioning, interfering with potential therapeutic designs. This study evaluates the effect of cell density versus passaging number on the proliferation rate of cord blood (CB)-USSCs, reflected on the telomere length, pluripotent transcription factors expression, and differentiation potential. Methodology: CB-USSCs were cultured at seeding densities of 5000, 500, 50, 5 cells/cm2. Cells from different passages of each seeding density were subjected to pluripotency genes (Oct4, Sox2, Nanog, klf4, c-Myc) and PDGFRa gene expression analysis, measurement of absolute telomere length by real-time PCR, and induction of differentiation into osteogenic, adipogenic, and chondrogenic lineages. Proliferation rate was expressed as population doubling (PD) and cumulative PD (CPD). Results: USSCs from earlier passages (P7) cultured at 5000 cells/cm2 showed the highest telomere length with high expression of pluripotency, and proliferation genes which decreased gradually with passaging till reaching their lowest level at P11 Moreover, their PD at P7 was 3 and CPD (P7-P11) was 12.8. USSCs cultured at 5 cells/cm^2 showed PD 12.9 at P7, with a higher expression of gene that plays an important role in proliferation (PDGFRa) than that of 5000 cells/cm2 at P7. Differentiation potentiality of 5000 cells/ cm2 at P7 was high with loss of differentiation at P11, while differentiation potentiality of 5 cells/ cm2 at P7 was much lower than that of 5000 cells/ cm2 at same passage. Conclusion: Taken together, the above results suggest the use of USSCs at earlier passages of 5 cells/cm2 cultures if a high expansion rate of CB-USSCs is required in therapeutic strategies, while USSCs culture at 5000 cells/cm2 is the best protocol if the therapeutic target is induction of USSCs differentiation.

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Transcatheter Aortic Valve Implantation (TAVI), the evolution, the 2nd generation the directions & the criterias of the future generations

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Abstract

Transcatheter valve intervention are more advanced and also successful evolution of conventional cardiac surgery. The first step in cardiac surgery was performed on the beating hearts in the case of digital or instrumental mitral commisurotomy. Although open heart surgery stays always the “Gold Standard” procedure, because it is crucial in understanding via direct