Stem Cell and Apoptosis Research Literatures

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Abstract: The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell. This article introduces recent research reports as references in the stem cell and apoptosis and related studies.
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Key words: stem cell; apoptosis; life; research; literature

Introduction

The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell.

The following introduces recent reports as references in the related studies.

Barcaui, C. B., A. M. Goncalves da Silva, et al. "Stem cell apoptosis in HIV-1 alopecia." J Cutan Pathol. 2006 Oct;33(10):667-71.

BACKGROUND: Diffuse alopecia occurs in almost 7% of HIV-1-infected patients. Telogen effluvium is the main pathogenic mechanism involved. Apoptotic keratinocytes in the outer root sheath at bulge level was described as the most characteristic histopathologic finding of this kind of hair loss. METHODS: A case-control study was conducted to investigate the occurrence of apoptosis of follicular stem cells at the bulge in diffuse alopecia of HIV-1 infection. We applied a double-staining procedure to transverse scalp sections from 15 HIV-1-infected patients and 12 controls, with the monoclonal antibody anticytokeratin 19 as stem cell marker and TUNEL technique to identify apoptosis. RESULTS: Eighty percent of cases and 25% of controls presented at least one double-stained follicle. The proportion of positive follicles per section was 48% (+/-7%) for cases and 26% (+/-13%) for controls. CONCLUSION: Our study demonstrated that diffuse alopecia related to HIV-1 infection represents a hair cycle disturbance and that part of the follicular stem cell population become apoptotic in a higher proportion than normal subjects. We found no cytotoxic folliculitis. Owing to its cell-cycle interaction and caspase-induction capacities, we propose HIV-1 viral protein R as a possible follicular stem cell apoptosis inductor.

Bironaite, D., D. Baltriukiene, et al. "Role of MAP kinases in nitric oxide induced muscle-derived adult stem cell apoptosis." Cell Biol Int. 2009 Jul;33(7):711-9. doi: 10.1016/j.cellbi.2009.03.007. Epub 2009 Apr 17.

Apoptosis in heart failure has been intensively investigated in vitro and in vivo. Stem cells have therapeutic value in the direct treatment of diseases, including cardiovascular disease. The main drawback of stem cell therapy is their poor survival in the diseased tissues. Since intracellular mitogen-activated protein kinases (MAPKs) actively participate in the regulation of cell survival and of proapoptotic signals, the ability to manipulate the mechanisms of MAPKs activation in myogenic stem cells might increase the survival of transplanted stem cells. Our results clearly demonstrate sustained activation of all three MAPKs, ERK, JNK and p38 in myogenic stem cells after exposure to the NO inducer, NOC-18. Inhibition of MAPKs phosphorylation by specific inhibitors revealed the anti-apoptotic role of MAPKs in myogenic stem cells.

Chen, L., H. Li, et al. "[Active ingredients of Plastrum Testudinis inhibit epidermal stem cell apoptosis in serum-deprived culture]." Zhong Xi Yi Jie He Xue Bao. 2011 Aug;9(8):888-93.

OBJECTIVE: To investigate the effects of active ingredients of Plastrum Testudinis (PT) on serum deprivation-induced apoptosis of epidermal stem cells (ESCs). METHODS: ESCs were isolated from the back skin of fetal Sprague-Dawley rats with 2

weeks of gestational age and were divided into normal group (10% fetal bovine serum), control group (serum-deprived culture) and groups treated with serum deprivation plus active ingredients of PT, including ethyl acetate extract (2B), stearic acid ethyl ester (S6), tetradecanoic acid sterol ester (S8) and (+)-4-cholesten-3-one (S9). The vitality of ESCs after 24, 48 and 72 h of culture was measured with MTT method; apoptotic ESCs double-stained with Annexin V-FITC and propidium iodine were detected by flow cytometry (FCM); Bcl-2 and caspase-3 expressions were measured by Western blotting. RESULTS: MTT results indicated that the vitality of ESCs in the active ingredients of PT groups at 48 h was increased compared with the control group and 2B had better effects than the others. FCM results indicated that 2B had the most significant anti-apoptotic effect compared with the control as well as S6, S8 and S9. Western blot results indicated that 2B, S6, S8 and S9 up-regulated the expression of Bcl-2 protein and down-regulated the expression of caspase-3 protein compared with the control. CONCLUSION: Ethyl acetate extract of Plastrum Testudinis inhibits epidermal stem cell apoptosis in serum-deprived culture by regulating the expressions of Bcl-2 and caspase-3 proteins and has a stronger anti-apoptotic effect than its constituents S6, S8 and S9.

Crisostomo, P. R., M. Wang, et al. "Gender differences in injury induced mesenchymal stem cell apoptosis and VEGF, TNF, IL-6 expression: role of the 55 kDa TNF receptor (TNFR1)." J Mol Cell Cardiol. 2007 Jan;42(1):142-9. Epub 2006 Oct 30.

Concomitant pro- and anti-inflammatory properties of bone marrow stem cells (BMSC) may be an important aspect of their ability to heal injured tissue. However, very few studies have examined whether gender differences exist in BMSC function. Indeed, it remains unknown whether gender differences exist in BMSC function and ability to resist apoptosis, and if so, whether TNF receptor 1 (TNFR1) plays a role in these differences. We hypothesized that TNFR1 ablation equalizes gender differences in bone marrow mesenchymal stem cell (MSC) apoptosis, as well as expression of vascular endothelial growth factor (VEGF), TNF and interleukin (IL)-6. Mouse MSCs from male wild type (WT), female WT, male TNFR1 knockouts (TNFR1KO) and female TNFR1KO were stressed by endotoxin 200 ng/ml or 1 h hypoxia. MSC activation was determined by measuring VEGF, TNF and IL-6 production (ELISA). Differences considered significant if $p<0.05$. LPS and hypoxia resulted in significant activation in all experimental groups compared to controls. Male WT demonstrated significantly greater TNF and IL-6 and significantly less VEGF release than female WT MSCs. However, release of TNF, IL-6 and VEGF in male TNFR1 knockouts differed from male WT, but was not different from female WT MSCs. Similarly apoptosis in hypoxic male TNFRIKO differed from male WT, but it was not different from apoptosis from WT female. Female WT did not differ in TNF, IL-6 and VEGF release compared to female TNFR1KO. Gender differences exist in injury induced BMSC VEGF, TNF and IL-6 expression. TNFR1 may autoregulate VEGF, TNF and IL-6 expression in males more than females. MSCs are novel therapeutic agents for organ protection, but further study of the disparate expression of VEGF, TNF and IL-6 in males and females as well as the role of TNFR1 in these gender differences is necessary to maximize this protection.

Deng, X., Q. Luan, et al. "Nanosized zinc oxide particles induce neural stem cell apoptosis." Nanotechnology. 2009 Mar 18;20(11):115101. doi: 10.1088/0957-4484/20/11/115101. Epub 2009 Feb 24.

Given the intensive application of nanoscale zinc oxide (ZnO) materials in our life, growing concerns have arisen about its unintentional health and environmental impacts. In this study, the neurotoxicity of different sized ZnO nanoparticles in mouse neural stem cells (NSCs) was investigated. A cell viability assay indicated that ZnO nanoparticles manifested dose-dependent, but no size-dependent toxic effects on NSCs. Apoptotic cells were observed and analyzed by confocal microscopy, transmission electron microscopy examination, and flow cytometry. All the results support the viewpoint that the ZnO nanoparticle toxicity comes from the dissolved Zn(2+) in the culture medium or inside cells. Our results highlight the need for caution during the use and disposal of ZnO manufactured nanomaterials to prevent the unintended environmental and health impacts.

Estrada-Bernal, A., K. Palanichamy, et al. "Induction of brain tumor stem cell apoptosis by FTY720: a potential therapeutic agent for glioblastoma." Neuro Oncol. 2012 Apr;14(4):405-15. doi: 10.1093/neuonc/nos005. Epub 2012 Feb 20.

FTY720 is a sphingosine analogue that down regulates expression of sphingosine-1-phosphate receptors and causes apoptosis of multiple tumor cell types, including glioma cells. This study examined the effect of FTY720 on brain tumor stem cells (BTSCs) derived from human glioblastoma (GBM) tissue. FTY720 treatment of BTSCs led to rapid inactivation of ERK MAP kinase, leading to upregulation of the BH3-only protein Bim and apoptosis. In combination with temozolomide (TMZ), the current standard chemotherapeutic agent for GBM, FTY720 synergistically induced BTSC apoptosis. FTY720 also

slowed growth of intracranial xenograft tumors in nude mice and augmented the therapeutic effect of TMZ, leading to enhanced survival. Furthermore, the combination of FTY720 and TMZ decreased the invasiveness of BTSCs in mouse brains. FTY720 is known to cross the blood-brain barrier and recently received Food and Drug Administration approval for treatment of relapsing multiple sclerosis. Thus, FTY720 is an excellent potential therapeutic agent for treatment of GBM.

Fuchs, Y., S. Brown, et al. "Sept4/ARTS regulates stem cell apoptosis and skin regeneration." Science. 2013 Jul 19;341(6143):286-9. doi: 10.1126/science.1233029. Epub 2013 Jun 20.

Adult stem cells are essential for tissue homeostasis and wound repair. Their proliferative capacity must be tightly regulated to prevent the emergence of unwanted and potentially dangerous cells, such as cancer cells. We found that mice deficient for the proapoptotic Sept4/ARTS gene have elevated numbers of hair follicle stem cells (HFSCs) that are protected against apoptosis. Sept4/ARTS(-/-) mice display marked improvement in wound healing and regeneration of hair follicles. These phenotypes depend on HFSCs, as indicated by lineage tracing. Inactivation of XIAP, a direct target of ARTS, abrogated these phenotypes and impaired wound healing. Our results indicate that apoptosis plays an important role in regulating stem cell-dependent regeneration and suggest that this pathway may be a target for regenerative medicine.

Garcia-Fernandez, M., H. Kissel, et al. "Sept4/ARTS is required for stem cell apoptosis and tumor suppression." Genes Dev. 2010 Oct 15;24(20):2282-93. doi: 10.1101/gad.1970110.

Inhibitor of Apoptosis Proteins (IAPs) are frequently overexpressed in tumors and have become promising targets for developing anti-cancer drugs. IAPs can be inhibited by natural antagonists, but a physiological requirement of mammalian IAP antagonists remains to be established. Here we show that deletion of the mouse Sept4 gene, which encodes the IAP antagonist ARTS, promotes tumor development. Sept4-null mice have increased numbers of hematopoietic stem and progenitor cells, elevated XIAP protein, increased resistance to cell death, and accelerated tumor development in an Emu-Myc background. These phenotypes are partially suppressed by inactivation of XIAP. Our results suggest that apoptosis plays an important role as a frontline defense against cancer by restricting the number of normal stem cells.

Geng, Y. J. "Molecular mechanisms for cardiovascular stem cell apoptosis and growth in the hearts with atherosclerotic coronary disease and ischemic heart failure." Ann N Y Acad Sci. 2003 Dec;1010:687-97.

In the heart with atherosclerotic coronary disease, chronic ischemia causes progressive loss of cardiovascular cells and ultimately triggers myocardial dysfunctions or heart failure. Various types of stem cells from embryonic and adult tissues have potentials for regenerating functional cardiovascular cells in the heart undergoing ischemic injury. However, native or exogenous stem cells in the ischemic hearts are exposed to various proapoptotic or cytotoxic factors. Furthermore, during repopulation and differentiation, certain numbers of newly produced cells may die by apoptosis during neocardiovascular tissue remodeling and morphogenesis. Embryonic and adult stem cells may have different life spans, as being programmed genetically to apoptosis. The endogenous and environmental factors play important roles in regulation of stem cells, including inflammatory cytokines, growth factors, surface receptors, proteolytic enzymes, mitochondrial respiration, nuclear proteins, telomerase activities, hypoxia-responding proteins, and stem cell-host cell interaction. Clarification of the molecular mechanisms may help us understand and design stem cell therapies.

Hao, Y. W., H. M. Xu, et al. "[Influence of reactive oxygen species on mouse bone marrow hematopoietic stem cell apoptosis]." Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2013 Oct;21(5):1237-42. doi: 10.7534/j.issn.1009-2137.2013.05.031.

Objective of this study was to investigate the mechanism of the biological function damage resulting from increased ROS in peripheral blood stem cells during peripheral blood stem cell transplantation. Bone marrow hematopoietic stem cells (BMHSC) were cultured at the oxygen concentration imitated according to the bone marrow oxygen concentration (5% O2) including mean venous oxygen concentration (12% O2), mean arterial oxygen concentration (20% O2). The ROS level in BMHSC was detected by using fluorescent probe, the percentage of BM-HSC in cell cycle was determined by flow cytometry, the apoptosis rate was assayed by Annexin V/PI double staining, the expression levels of ATM gene and P21 protein were measured by PCR and Western respectively. The results showed that as compared with control group (5% O2), the ROS levels were lower, the percentage of cells in G1, S,G2/M phase increased ($P < 0.01$), the apoptosis rate of cells obviously increased ($P < 0.01$), the expression level of ATM gene obviously decreased ($P < 0.01$), while the expression level of P21 protein significantly was enhanced ($P < 0.01$) in 12% O2, 20% O2 and 5%-12%-20% O2 groups. It is concluded that

ROS results in the apoptosis of BMHSC through inhibiting the expression of ATM gene and activating P21 protein.

Hicks, S. D. and M. W. Miller "Effects of ethanol on transforming growth factor Beta1-dependent and -independent mechanisms of neural stem cell apoptosis." Exp Neurol. 2011 Jun;229(2):372-80. doi: 10.1016/j.expneurol.2011.03.003. Epub 2011 Mar 16.

Stem cell vitality is critical for the growth of the developing brain. Growth factors can define the survival of neural stem cells (NSCs) and ethanol can affect growth factor-mediated activities. The present study tested two hypotheses: (a) ethanol causes the apoptotic death of NSCs and (b) this effect is influenced by the ambient growth factor. Monolayer cultures of non-immortalized NS-5 cells were exposed to fibroblast growth factor (FGF) 2 or transforming growth factor (TGF) beta1 in the absence or presence of ethanol for 48 h. Ethanol killed NSCs as measured by increases in the numbers of ethidium bromide+ and annexin V+ cells and decreases in the number of calcein AM+ (viable) cells. These toxic effects were promoted by TGFbeta1. A quantitative polymerase chain reaction array of apoptosis-related mRNAs revealed an ethanol-induced increase (>/=2-fold change; $p<0.05$) in transcripts involved in Fas ligand (FasL) and tumor necrosis factor (TNF) signaling. These effects, particularly the FasL pathway, were potentiated by TGFbeta1. Immunocytochemical analyses of NS-5 cells showed that transcriptional alterations translated into consistent up-regulation of protein expression. Experiments with the neocortical proliferative zones harvested from fetal mice exposed to ethanol showed that ethanol activated similar molecular systems in vivo. Thus, ethanol induces NSC death through two distinct molecular mechanisms, one is initiated by TGFbeta1 (FasL) and another (through TNF) which is TGFbeta1-independent.

Hou, Y. S., L. Y. Liu, et al. "Lipopolysaccharide pretreatment inhibits LPS-induced human umbilical cord mesenchymal stem cell apoptosis via upregulating the expression of cellular FLICE-inhibitory protein." Mol Med Rep. 2015 Aug;12(2):2521-8. doi: 10.3892/mmr.2015.3723. Epub 2015 May 4.

Mesenchymal stem cell (MSC)-based regenerative therapy is currently regarded as a novel approach with which to repair damaged tissues. However, the efficiency of MSC transplantation is limited due to the low survival rate of engrafted MSCs. Lipopolysaccharide (LPS) production is increased in numerous diseases and serves an essential function in the regulation of apoptosis in a variety of cell types. Previous studies have indicated that lowdose LPS pretreatment contributes to cytoprotection. In the current study, LPS was demonstrated to induce apoptosis in human umbilical cord mesenchymal stem cells (hUCMSCs) via the activation of caspase, in a dosedependent manner. Lowdose LPS pretreatment may protect hUCMSCs against apoptosis induced by highdose LPS, by upregulating the expression of cellular FADDlike IL1betaconverting enzymeinhibitory protein (cFLIP). The results of the present study indicate that pretreatment with an appropriate concentration of LPS may alleviate high-dose LPS-induced apoptosis.

Kearney, E. M., P. J. Prendergast, et al. "Mechanisms of strain-mediated mesenchymal stem cell apoptosis." J Biomech Eng. 2008 Dec;130(6):061004. doi: 10.1115/1.2979870.

Mechanical conditioning of mesenchymal stem cells (MSCs) has been adopted widely as a biophysical signal to aid tissue engineering applications. The replication of in vivo mechanical signaling has been used in in vitro environments to regulate cell differentiation, and extracellular matrix synthesis, so that both the chemical and mechanical properties of the tissue-engineered construct are compatible with the implant site. While research in these areas contributes to tissue engineering, the effects of mechanical strain on MSC apoptosis remain poorly defined. To evaluate the effects of uniaxial cyclic tensile strain on MSC apoptosis and to investigate mechanotransduction associated with strain-mediated cell death, MSCs seeded on a 2D silicone membrane were stimulated by a range of strain magnitudes for 3 days. Mechanotransduction was investigated using the stretch-activated cation channel blocker gadolinium chloride, the L-type voltage-activated calcium channel blocker nicardipine, the c-jun NH(2)-terminal kinase (JNK) blocker D-JNK inhibitor 1, and the calpain inhibitor MDL 28170. Apoptosis was assessed through DNA fragmentation using the terminal deoxynucleotidyl transferase mediated-UTP-end nick labeling method. Results demonstrated that tensile strains of 7.5% or greater induce apoptosis in MSCs. L-type voltage-activated calcium channels coupled mechanical stress to activation of calpain and JNK, which lead to apoptosis through DNA fragmentation. The definition of the in vitro boundary conditions for tensile strain and MSCs along with a proposed mechanism for apoptosis induced by mechanical events positively contributes to the development of MSC biology, bioreactor design for tissue engineering, and development of computational methods for mechanobiology.

Liu, X., B. Duan, et al. "SDF-1/CXCR4 axis modulates bone marrow mesenchymal stem cell

apoptosis, migration and cytokine secretion." Protein Cell. 2011 Oct;2(10):845-54. doi: 10.1007/s13238-011-1097-z. Epub 2011 Nov 6.

Bone marrow mesenchymal stem cells (MSCs) are considered as a promising cell source to treat the acute myocardial infarction. However, over 90% of the stem cells usually die in the first three days of transplantation. Survival potential, migration ability and paracrine capacity have been considered as the most important three factors for cell transplantation in the ischemic cardiac treatment. We hypothesized that stromal-derived factor-1 (SDF-1)/CXCR4 axis plays a critical role in the regulation of these processes. In this study, apoptosis was induced by exposure of MSCs to H(2)O(2) for 2 h. After re-oxygenation, the SDF-1 pretreated MSCs demonstrated a significant increase in survival and proliferation. SDF-1 pretreatment also enhanced the migration and increased the secretion of pro-survival and angiogenic cytokines including basic fibroblast growth factor and vascular endothelial growth factor. Western blot and RT-PCR demonstrated that SDF-1 pretreatment significantly activated the pro-survival Akt and Erk signaling pathways and up-regulated Bcl-2/Bax ratio. These protective effects were partially inhibited by AMD3100, an antagonist of CXCR4.We conclude that the SDF-1/CXCR4 axis is critical for MSC survival, migration and cytokine secretion.

Liu, Z., H. Liu, et al. "PDGF-BB and bFGF ameliorate radiation-induced intestinal progenitor/stem cell apoptosis via Akt/p53 signaling in mice." Am J Physiol Gastrointest Liver Physiol. 2014 Dec 1;307(11):G1033-43. doi: 10.1152/ajpgi.00151.2014. Epub 2014 Oct 9.

Radiation-induced gastrointestinal (GI) syndrome currently has no effective prophylactic or therapeutic treatment. Previous studies and our data have demonstrated the important role of p53 in acute radiation-induced GI syndrome in mice. Many cytokines, such as tumor necrosis factor-alpha and fibroblast growth factor (bFGF), have been found to protect against radiation-induced intestinal injury, although the underlying mechanisms remain to be identified. Here, we report blockage of p53 through a protein kinase B (Akt) pathway in intestinal progenitor/stem cells or crypt cells as a novel molecular mechanism of growth factor-mediated intestinal radioprotection. Treatment with platelet-derived growth factor (PDGF-BB) or bFGF activated Akt phosphorylation in the intestinal crypt, lessened intestinal crypt p53 expression, decreased radiation-induced apoptosis in mouse intestinal progenitor/stem cell marker leucine-rich repeat-containing G protein-coupled receptor 5 (Lgr5)-positive cells by an average of 50%, and increased the survival rate of mice with abdominal radiation by 3 days in average. Conversely, the Akt inhibitor perifosine obstructed growth factor-simulated Akt phosphorylation while promoting radiation-induced p53 expression in intestinal crypts. Importantly, reduced Akt phosphorylation and elevated p53 expression due to the Akt inhibitor perifosine impaired intestinal progenitor/stem cells radioprotection provided by PDGF-BB and bFGF. Consistently, PDGF-BB and bFGF both upregulated Akt activation, suppressed radiation-induced p53 expression, and abrogated radiation-induced apoptosis in IEC-6 cells, although p53 overexpression in IEC-6 cells partially counteracted the radioprotection of PDGF-BB and bFGF. Our data suggest that intestinal crypt radioprotection by PDGF-BB and bFGF is dependent on regulation of Akt/p53 signaling.

Lucas, T., B. Pratscher, et al. "The human orthologue of a novel apoptosis response gene induced during rat myelomonocytic stem cell apoptosis maps to 20q13.12." Stem Cells Dev. 2005 Oct;14(5):556-63.

Stem cell factor (SCF) stimulation of the receptor tyrosine kinase c-kit has effects on the proliferation, differentiation, and apoptotic regulation of hematopoietic progenitor cell populations. Rat bone marrow myelomonocytic stem cells (MSC) isolated in vitro by wheat germ agglutinin culture exclusively undergo self-renewal divisions when stimulated by SCF but bipotentially differentiate in the presence of dexamethasone or 1alpha,25-dihydroxyvitamin D(3) to granulocytes and macrophages, respectively. We show here that withdrawal of SCF from MSC induces rapid apoptosis in all stages of the cell cycle accompanied by development of an ultrastructural apoptotic morphology. To investigate immediate-early gene induction during MSC apoptosis, a differential display polymerase chain reaction (DD-PCR) screen coupled with rapid amplification of cDNA ends (RACE) PCR was performed. An immediate-early apoptosis response gene was isolated from growth factor-deprived MSC that was not expressed during self-renewal or differentiation induction cultures containing SCF. The protein contains a PEST region enriched in proline, glutamic acid, serine, and threonine residues common to proteins with a high turnover and has a cytoplasmic, vesicular localization in apoptotic MSC shown by immunohistochemistry. The human orthologous gene, isolated by RACE PCR, shows 86% homology to the rat protein and high similarity with a human uncharacterized hypothalamus predicted protein (HSMNP1) localized to the long arm of chromosome 20. Because deletions in this region are a common occurrence in a wide range of myeloproliferative disorders characterized by treatment resistance to apoptosis, HSMNP1 expression

may play a role in normal and pathological myeloid development.

Nejadnik, H., D. Ye, et al. "Magnetic resonance imaging of stem cell apoptosis in arthritic joints with a caspase activatable contrast agent." ACS Nano. 2015 Feb 24;9(2):1150-60. doi: 10.1021/nn504494c. Epub 2015 Jan 26.

About 43 million individuals in the U.S. encounter cartilage injuries due to trauma or osteoarthritis, leading to joint pain and functional disability. Matrix-associated stem cell implants (MASI) represent a promising approach for repair of cartilage defects. However, limited survival of MASI creates a significant bottleneck for successful cartilage regeneration outcomes and functional reconstitution. We report an approach for noninvasive detection of stem cell apoptosis with magnetic resonance imaging (MRI), based on a caspase-3-sensitive nanoaggregation MRI probe (C-SNAM). C-SNAM self-assembles into nanoparticles after hydrolysis by caspase-3, leading to 90% amplification of (1)H MR signal and prolonged in vivo retention. Following intra-articular injection, C-SNAM causes significant MR signal enhancement in apoptotic MASI compared to viable MASI. Our results indicate that C-SNAM functions as an imaging probe for stem cell apoptosis in MASI. This concept could be applied to a broad range of cell transplants and target sites.

Seo, B. N., J. M. Ryu, et al. "Delphinidin prevents hypoxia-induced mouse embryonic stem cell apoptosis through reduction of intracellular reactive oxygen species-mediated activation of JNK and NF-kappaB, and Akt inhibition." Apoptosis. 2013 Jul;18(7):811-24. doi: 10.1007/s10495-013-0838-2.

Delphinidin, gallic acid, betulinic acid, and ursolic acid, which are bio-active ingredients in a variety of fruits, vegetables, and herbs, have potent antioxidant activity and various biological activities. However, it is not clear whether these bio-active ingredients can significantly contribute to the protection of embryonic stem (ES) cells from hypoxia-induced apoptosis. In the present study, hypoxia-induced ES cells apoptosis with time, which were abrogated by pretreatment with all ingredients. Hypoxia-induced ROS generation was blocked by pretreatment with all ingredients in a dose-dependent manner, with the maximum ROS scavenging effect observed for delphinidin. Hypoxia increased phosphorylation of JNK and NF-kappaB were blocked by pretreatment of delphinidin as well as NAC. Hypoxia decreased phosphorylation of Akt(thr308) and (ser473); these decreases were reversed by pretreatment with delphinidin or NAC. However, Akt inhibition did not affect NF-kappaB phosphorylation. Delphinidin attenuated the hypoxia-induced increase in Bax, cleaved caspase-9, cleaved caspase-3, and decrease in Bcl-2, which were diminished by pretreatment of Akt inhibitor. Hypoxia induced Bax translocation from the cytosol to mitochondria. Furthermore, hypoxia induced mitochondria membrane potential loss and cytochrome c release in cytosol, which were blocked by delphinidin pretreatment. Hypoxia induced cleavage of procaspase-9 and procaspase-3 which were blocked by delphinidin or SP600125, but Akt inhibitor abolished the protection effect of delphinidin. Moreover, inhibition of JNK and NF-kappaB abolished hypoxia-induced ES cell apoptosis and inhibition of Akt attenuated delphinidin-induced blockage of apoptosis. The results indicate that delphinidin can prevent hypoxia-induced apoptosis of ES cells through the inhibition of JNK and NF-kappaB phosphorylation, and restoration of Akt phosphorylation.

Shimozato, O., J. R. Ortaldo, et al. "Impaired NK cell development in an IFN-gamma transgenic mouse: aberrantly expressed IFN-gamma enhances hematopoietic stem cell apoptosis and affects NK cell differentiation." J Immunol. 2002 Feb 15;168(4):1746-52.

Aberrant expression of IFN-gamma has been demonstrated to cause a wide variety of alterations in cell function and development. Previously we reported that constitutive expression of IFN-gamma in bone marrow (BM) and thymus results in a total absence of B cells and a substantial decrease in the number of hematopoietic progenitor cells. In this study, we demonstrate a severe deficiency of NK1.1(+)CD3(-) cells in this transgenic mouse model. Compared with normal control littermates, we found a pronounced reduction of NK cells in IFN-gamma transgenic mouse spleen and liver despite maintenance of normal function. In addition, we observed a reduced number of BM cells in the IFN-gamma transgenic mouse despite normal expression of hematopoietic growth factors in the BM. Interestingly, these cells were less responsive to stem cell factor (SCF) despite c-kit expression on hematopoietic stem cells (HSCs). We observed that addition of exogenous IFN-gamma inhibited proliferation of HSCs and differentiation of NK precursors from HSCs in normal mice in response to SCF, IL-7, fms-like tyrosine kinase 3 ligand, and IL-15. Furthermore, we found that HSCs express the IFN-gammaRalpha subunit and undergo apoptosis in response to exogenous IFN-gamma. Thus, we have demonstrated the occurrence of a severe deficiency of NK cells and lower numbers of BM cells in an IFN-gamma transgenic mouse model. Furthermore, because exogenous IFN-gamma affects the responsiveness to hematopoietic growth factors such as SCF in vitro, our

results indicate that chronic expression of IFN-gamma in vivo leads to widespread immune system defects, including alterations in NK cell differentiation.

Sokolowski, K., M. Obiorah, et al. "Neural stem cell apoptosis after low-methylmercury exposures in postnatal hippocampus produce persistent cell loss and adolescent memory deficits." Dev Neurobiol. 2013 Dec;73(12):936-49. doi: 10.1002/dneu.22119. Epub 2013 Sep 30.

The developing brain is particularly sensitive to exposures to environmental contaminants. In contrast to the adult, the developing brain contains large numbers of dividing neuronal precursors, suggesting that they may be vulnerable targets. The postnatal day 7 (P7) rat hippocampus has populations of both mature neurons in the CA1-3 region as well as neural stem cells (NSC) in the dentate gyrus (DG) hilus, which actively produce new neurons that migrate to the granule cell layer (GCL). Using this well-characterized NSC population, we examined the impact of low levels of methylmercury (MeHg) on proliferation, neurogenesis, and subsequent adolescent learning and memory behavior. Assessing a range of exposures, we found that a single subcutaneous injection of 0.6 microg/g MeHg in P7 rats induced caspase activation in proliferating NSC of the hilus and GCL. This acute NSC death had lasting impact on the DG at P21, reducing cell numbers in the hilus by 22% and the GCL by 27%, as well as reductions in neural precursor proliferation by 25%. In contrast, non-proliferative CA1-3 pyramidal neuron cell number was unchanged. Furthermore, animals exposed to P7 MeHg exhibited an adolescent spatial memory deficit as assessed by Morris water maze. These results suggest that environmentally relevant levels of MeHg exposure may decrease NSC populations and, despite ongoing neurogenesis, the brain may not restore the hippocampal cell deficits, which may contribute to hippocampal-dependent memory deficits during adolescence.

Sui, Y., Z. Zhao, et al. "Adenosine monophosphate-activated protein kinase activation enhances embryonic neural stem cell apoptosis in a mouse model of amyotrophic lateral sclerosis." Neural Regen Res. 2014 Oct 1;9(19):1770-8. doi: 10.4103/1673-5374.143421.

Alterations in embryonic neural stem cells play crucial roles in the pathogenesis of amyotrophic lateral sclerosis. We hypothesized that embryonic neural stem cells from SOD1(G93A) individuals might be more susceptible to oxidative injury, resulting in a propensity for neurodegeneration at later stages. In this study, embryonic neural stem cells obtained from human superoxide dismutase 1 mutant (SOD1(G93A)) and wild-type (SOD1(WT)) mouse models were exposed to H2O2. We assayed cell viability with mitochondrial succinic dehydrogenase colorimetric reagent, and measured cell apoptosis by flow cytometry. Moreover, we evaluated the expression of the adenosine monophosphate-activated protein kinase (AMPK) alpha-subunit, paired box 3 (Pax3) protein, and p53 in western blot analyses. Compared with SOD1(WT) cells, SOD1(G93A) embryonic neural stem cells were more likely to undergo H2O2-induced apoptosis. Phosphorylation of AMPKalpha in SOD1(G93A) cells was higher than that in SOD1(WT) cells. Pax3 expression was inversely correlated with the phosphorylation levels of AMPKalpha. p53 protein levels were also correlated with AMPKalpha phosphorylation levels. Compound C, an inhibitor of AMPKalpha, attenuated the effects of H2O2. These results suggest that embryonic neural stem cells from SOD1(G93A) mice are more susceptible to apoptosis in the presence of oxidative stress compared with those from wild-type controls, and the effects are mainly mediated by Pax3 and p53 in the AMPKalpha pathway.

Zhang, X. M., G. W. Huang, et al. "Folate deficiency induces neural stem cell apoptosis by increasing homocysteine in vitro." J Clin Biochem Nutr. 2009 Jul;45(1):14-9. doi: 10.3164/jcbn.08-223. Epub 2009 Jun 30.

Cellular events for neural progenitor cells, such as proliferation and differentiation, are regulated by multiple intrinsic and extrinsic cell signals. Folate plays a central role in central nervous system development, so folate, as an extrinsic signal, may affect neural stem cell (NSC) proliferation and differentiation. In the present study, we investigated the effects of folate deficiency on the cell proliferation, cell apoptosis and homocysteine concentrations in NSCs. NSCs were isolated from fetal rats and identified as NSCs by their expression of immunoreactive nestin. Cell proliferation was quantitated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. Apoptotic cells were detected and confirmed by flow cytometric analysis. We measured homocysteine concentrations in NSCs by high performance liquid chromatography and detected the expression of caspase-3 by western blot method. Folate deficiency not only decreased cell proliferation, but also increased the apoptotic rate of NSCs as demonstrated by the increased expression of early apoptotic markers such as caspase-3, compared to control group ($p<0.05$). Furthermore, There was a statistically significant increase in homocysteine concentration during folate deficiency in NSCs ($p<0.05$). These data suggest that folate affects the cell

proliferation, apoptosis and homocysteine generation in NSC cells.

Zhou, L., J. Opalinska, et al. "p38 MAP kinase regulates stem cell apoptosis in human hematopoietic failure." Cell Cycle. 2007 Mar 1;6(5):534-7. Epub 2007 Mar 25.

Myelodysplastic syndromes (MDS) are clonal stem cell disorders that lead to ineffective hematopoiesis and are common causes of low blood counts in the elderly. The exact molecular mechanisms regulating increased stem apoptosis in these disorders are not well defined. p38 MAPK activation is important in regulating the growth inhibitory signals of TNF-alpha, TGF-beta and Interferons on human hematopoiesis. Our findings show that p38 MAPK is overactivated in myelodysplasia bone marrows and regulates hematopoietic stem cell apoptosis. Inhibition of p38 MAPK by genetic or pharmacologic means decreases apoptosis and stimulates in vitro hematopoiesis from primary MDS hematopoietic progenitors. These studies point to the potential efficacy of selective p38alpha inhibitor, SCIO-469, in human bone marrow failure.

Zou, W. W., H. P. Xiao, et al. "Propofol induces rat embryonic neural stem cell apoptosis by activating both extrinsic and intrinsic pathways." Mol Med Rep. 2013 Apr;7(4):1123-8. doi: 10.3892/mmr.2013.1298. Epub 2013 Jan 29.

Propofol has previously been shown to have detrimental effects on the developing brain. Neural stem cells, identified in the embryonic brain as well as in the adult brain, are multipotent, self-renewing cells, which are capable of differentiating into different phenotypes of the nervous system. The present study was designed to investigate propofol-induced rat embryonic neural stem cell apoptosis and its potential mechanisms. Rat embryonic neural stem cells were isolated, cultured and characterized. Treatment of these cultured stem cells with different doses of propofol was carried out and cell proliferation was assessed by MTT assay and apoptosis by flow cytometric analysis. Cellular levels of active forms of caspase-3 and caspase-8, which regulate the extrinsic apoptotic pathway, and of caspase-9 and cytochrome C, which regulate the intrinsic apoptotic pathway, were detected by western blotting. Over 95% of isolated rat embryonic neural stem cells expressed the Nestin protein, as detected by immunofluorescence staining. Using an in vitro cell culture system, we showed that propofol inhibited cell growth and induced cell apoptosis in a dose-dependent manner. Furthermore, western blot analysis showed that propofol treatment significantly elevated levels of active forms of caspase-3, caspase-8, caspase-9 and cytochrome C in the embryonic neural stem cells. Propofol induced rat embryonic neural stem cell apoptosis and activated caspase-3, caspase-8, caspase-9 and cytochrome C, suggesting that propofol-induced stem cell apoptosis may be regulated through both the extrinsic and intrinsic apoptotic pathways.

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