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Mini Review Article

Novel Aspects of Oxidative Stress-Associated Carcinogenesis

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ABSTRACT

Oxidative stress is associated with carcinogenesis. Reactive oxygen and nitrogen species contribute to the accumulation of mutations in the genome, presumably followed by selective processes. Recent data suggest that preferred signaling pathways exist for oxidative stress–associated carcinogenesis. Whether this completely depends on random mutations induced by reactive species or whether instead some fragile genomic loci are sensitive to oxidative damage in association with changes of transcriptional activity or other topologic or nontopologic effects remains to be explored. Reliable markers for oxidative stress as well as for oxidative stress–induced preneoplastic lesions must be established. *Antioxid. Redox Signal.* 8, 1373–1377.

OXIDATIVE STRESS AND CANCER

Oxidative stress is associated with a variety of pathological phenomena, including inflammation, ultraviolet and γ-irradiation, toxicity of transition metals and certain chemotherapeutic agents, as well as ischemia–reperfusion injury. Epidemiologic studies indicate a strong association between chronically oxidative conditions and carcinogenesis: for example, the incidence of colorectal cancer is increased in ulcerative colitis (8); chronic *Helicobacter pylori* infection is associated with a high incidence of gastric cancer (9, 37); chronic tuberculous pleuritis causes a high incidence of malignant lymphoma (20); severe burn by ultraviolet radiation is a risk factor for skin cancer (12, 26); γ-irradiation causes a high incidence of leukemia (38); and asbestosis (asbestos fibers are rich in iron) is often associated with mesothelioma and lung carcinoma (17). At least under these circumstances, and probably in other types of carcinogenesis as well, oxidative stress appears to play a major role. Here, I briefly review recently established concepts and raise unanswered questions in this area.

Cancer is one of the leading causes of death in most developed countries. It is established that multiple stepwise alterations of the original genome information are responsible for carcinogenesis (45). Excess generation of reactive oxygen and nitrogen species can cause DNA damage and modifications (6, 33, 43, 47), leading to changes in the genomic information in spite of the robust counteractions of repair enzymes and apoptotic pathways. These changes of genetic information fall into the category of mutations. They include point mutations, deletions, insertions, or chromosomal translocations. These events may cause activation of oncogenes or inactivation of tumor-suppressor genes. Oncogene is now a classic term, meaning any gene that can be a causative factor via its activation in carcinogenesis or transformation. It is now realized that this definition is sometimes misleading, considering the fact that expression of these genes is required for tissue regeneration after injury. Tumor-suppressor genes may be classified into two broad categories: caretakers (DNA repair genes) and gatekeepers (cell-cycle inhibitors). Apoptosis-related genes are another class of cancer genes (50). After three decades of intensive search to identify the mutated genes (cancer genes) that are causally implicated in carcinogenesis, a "census" of cancer genes was recently performed. This study indicated that mutations in >1% of genes (291 cancer genes) contribute to human cancer (~80% dominant trait and ~20% recessive trait). Ninety percent of cancer genes show somatic mutations in cancer, 20% show germline mutations, and 10% show both. The most common domain that is encoded by cancer genes is the protein kinase. Several domains that are involved in DNA binding and transcriptional regulation are common in proteins that are encoded by cancer genes (10).

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SIGNALING PATHWAYS AND THEIR REGULATION

Imatinib mesylate (Gleevec), a tyrosine kinase inhibitor, has recently shown success in treating chronic myelogenous leukemia in which a chimeric oncogene, *bcr-abl,* is generated via chromosomal translocation (4), and inoperable gastrointestinal stromal tumor (21). Conversely, recombinant humanized anti-HER2/c-ErbB2/Neu antibody (Herceptin) (2) is now used clinically to antagonize the receptor-type tyrosine kinase in invasive ductal carcinoma of the mammary gland (42). These exciting advancements emphasize the importance of signaling pathways in cellular proliferation. However, we have to be aware that these target signaling pathways in cancer cells have evolved by selective processes from thousands of possible mutations to establish a "robust" system (24). Unfortunately, how cells acquired those mutations is largely unknown. The general significance of oxidative stress in carcinogenesis has been established in the past decade and is summarized in Fig. 1. Importantly, mutation and persistent activation of new signaling pathways for proliferation are interrelated. Selected mutations of oncogenes generate new signaling pathways, whereas increased cellular proliferation enhances the mutation rate. In a sense, carcinogenesis may be compared with evolution, with the difference that carcinogenesis is fatally impatient with time.

Redox regulation is one of the key mechanisms for adapting to a variety of stresses, including oxidative stress (40). Recently, it was reported from several independent laboratories that an antagonizing protein for thioredoxin (thioredoxin-binding protein-2, TBP-2; also as vitamin D_3 upregulated protein-1, VDUP-1) (28) is downregulated in cancers such as human adult T-cell leukemia (1, 27), human gastric cancer (14, 19), and rat iron-induced renal cell carcinoma (7). The mode of inactivation involves methylation of the promoter region (7). Furthermore, TBP-2 is expressed at higher levels in nonmetastatic melanomas than in metastatic melanomas (11). Studies of a TBP-2-null mutant mouse (3) provided evidence that loss of TBP-2 results in enhanced sulfhydryl reduction and dysregulated carbohydrate and lipid metabolism, namely hyperinsulinemia, hypoglycemia, hypertriglyceridemia, and increased levels of ketone bodies, at least in the liver and pancreatic β-cells (18). This has been confirmed by producing TBP-2–deficient mice (35). Loss of TBP-2 appears advantageous in cancer cells because it ultimately results in facilitation of the glycolytic pathway by enhancing the thioredoxin activity.

In renal tubular cells, TBP-2 is abundant in both mitochondria and nuclei (7). The mitochondrion is a key organelle that acts as a source of reactive oxygen species. The role of mitochondria in cancer was discussed in a recent forum of this journal (31). The form of superoxide dismutase present in mitochondria is manganese superoxide dismutase (MnSOD). Although some aspects of the role of MnSOD in cancer are still controversial, as discussed (15, 23, 32, 39, 52), it has been suggested that overexpression of this enzyme is a possible means of anticancer therapy (30, 36). Drugs that lead to TBP-2 and MnSOD expression would be promising as therapy for cancers that lack these pathways.

OXIDATIVE STRESS AND GENOME: OXYGENOMICS

Free radical reactions have been considered to have little specificity *in vitro,* in contrast to the extremely selective antigen–antibody interactions. For example, the second-order rate constant for the reaction of hydroxyl radical with guanine is ~1.0×10^{10} M/s (13). Thus, one might think that the genome is damaged at random and that no specific "target" genes or signaling pathways are found in oxidative stress-associated carcinogenesis. However, it may be time to revisit this doctrine. We challenged this hypothesis because ferric nitrilotriacetate (Fe-NTA)-induced renal cancers are rather homogeneous in histology (29, 47). We used a genetic strategy which revealed that *p15 INK4B (p15)* and *p16 INK4A (p16)* tumor-suppressor genes are two of the major target genes. This was the first report that showed the presence of a target gene in the free radical–induced carcinogenesis model (46). The biologic significance of this finding is enormous because *p16* is associated not only with the retinoblastoma protein pathway as a cyclin-dependent kinase 4 and 6 inhibitor, but also with the p53 pathway via $p19^{ARF}$ and MDM2 (22). $p19^{ARF}$ is an alternatively spliced transcript from the *p16* tumor-suppressor gene (5). Indeed, iron-mediated oxidative damage appears to attack one of the most critical sites of the genome. We later showed that allelic loss of *p16* occurs as early as 1 week after the start of the animal experiment and is gene specific (16). We believe

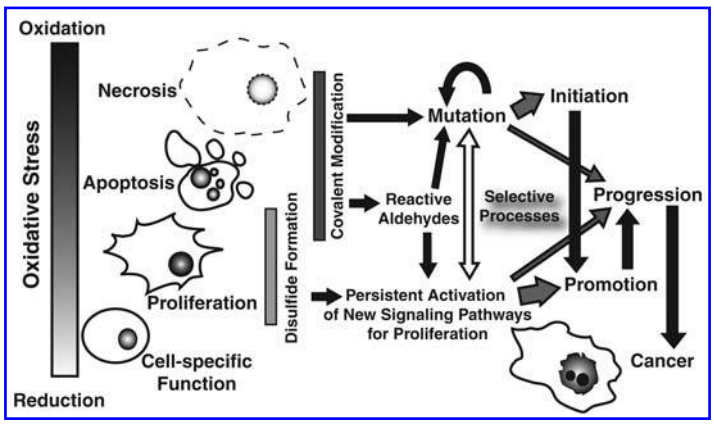

FIG. 1. Significance of oxidative stress in carcinogenesis. The left half of the figure shows the general cellular significance of oxidative stress, whereas the right half shows the significance in carcinogenesis as related to the classic concepts of initiation, promotion, and progression. The self-directed arrow at "Mutation" indicates "mutator phenotype" (25). Reactive aldehydes include 4-hydroxynonenal and other aldehydes (49). Refer to text for details.

that these results suggest the presence of fragile sites in the genome, because allelic loss of a tumor-suppressor gene does not necessarily mean loss of the signaling pathway if overriding events such as mutation or methylation of the promoter region do not occur at the remaining allele. Thus, the next question is whether carcinogenesis is a process of "random alteration of genetic information and selection" or "nonrandom alteration of genetic information and selection." The conclusion may change the chemopreventive strategy in particular cases of carcinogenesis.

Studying the localization of oxidative nucleic acid damage in comparison with genome information and cellular structure is becoming increasingly important. A plethora of data has been published on oxidative DNA damage *in vitro* by using purified DNA or cultured cells, and based on these data, it has been claimed that certain specific sequences including telomeres (34, 51) are especially vulnerable to oxidative damage. However, currently limited data are available on which part of the genome is susceptible to oxidative damage *in vivo* in individuals. The results obtained *in vitro* should be confirmed at the tissue and organ levels step by step. I believe that this is now possible, given the completion of genome projects of humans, mice, rats, and other species (48). One must be aware that nuclear genomic DNA in association with histones is integrated into the chromatin structure in the cell, and that some parts of the chromatin structure are open for transcription. It is possible that the genome areas susceptible to oxidative stress may differ depending on the kind of cell and the situation in which the cells are placed. Such difference could help to explain the different signaling pathways each type of cancer has acquired. As described earlier, tailored cancer therapy is now being developed. Cancer prevention (41, 44) is not less important than cancer therapy, considering the economic impact of current medical therapeutic costs. In the near future, tailored cancer prevention may become an important intervention. It will be essential to establish reliable markers for oxidative stress as well as for oxidative stress–induced preneoplastic lesions.

ABBREVIATIONS

Fe-NTA, ferric nitrilotriacetate; MDM, mouse double minute; MnSOD, manganese superoxide dismutase; TBP-2, thioredoxin binding protein-2.

REFERENCES

1. Ahsan M, Masutani H, Yamaguchi Y, Kim Y, Nosaka K, Matsuoka M, Nishinaka Y, Maeda M, and Yodoi J. Loss of interleukin-2-dependency in HTLV-I-infected T cells on gene silencing of thioredoxin-binding protein-2. *Oncogene* 25: 2181–2189, 2006.
2. Baselga J, Norton L, Albanell J, Kim Y, and Mendelsohn J. Recombinant humanized anti-HER2 antibody (Herceptin) enhances the antitumor activity of paclitaxel and doxorubicin against HER2/neu overexpressing human breast cancer xenografts. *Cancer Res* 58: 2825–2831, 1998.
3. Bodnar J, Chatterjee A, Castellani L, Ross D, Ohmen J, Cavalcoli J, Wu C, Dains K, Catanese J, Chu M, Sheth S, Charugundla K, Demant P, West D, de Jong P, and Lusis A. Positional cloning of the combined hyperlipidemia gene Hyplip1. *Nat Genet* 30: 110–116, 2002.
4. Capdeville R, Buchdunger E, Zimmermann J, and Matter A. Glivec (STI571, imatinib), a rationally developed, targeted anticancer drug. *Nat Rev Drug Discov* 1: 493–502, 2002.
5. Chan FK, Zhang J, Cheng L, Shapiro DN, and Winoto A. Identification of human and mouse p19, a novel CDK4 and CDK6 inhibitor with homology to $p16^{ink4}$. *Mol Cell Biol* 15: 2682–2688, 1995.
6. Dizdaroglu M. Chemical determination of free radical-induced damage to DNA. *Free Radic Biol Med* 10: 225–242, 1991.
7. Dutta KK, NIshinaka Y, Masutani H, Akatsuka S, Aung TT, Shirase T, Lee W-H, Hiai H, Yodoi J, and Toyokuni S. Thioredoxin-binding protein-2 is a target gene in oxidative stress-induced renal carcinogenesis. *Lab Invest* 85: 798–807, 2005.
8. Ekbom A, Helmick C, Zack M, and Adami H. Ulcerative colitis and colorectal cancer: A population-based study. *N Engl J Med* 323: 1228–1233, 1990.
9. Forman D, Newell D, Fullerton F, Yarnell J, Stacey A, Wald N, and Sitas F. Association between infection with *Helicobacter pylori* and risk of gastric cancer: Evidence from a prospective investigation. *BMJ* 302: 1302–1305, 1991.
10. Futreal P, Coin L, Marshall M, Down T, Hubbard T, Wooster R, Rahman N, and Stratton M. A census of human cancer genes. *Nat Rev Cancer* 4: 177–183, 2004.
11. Goldberg S, Miele M, Hatta N, Takata M, Paquette-Straub C, Freedman L, and Welch D. Melanoma metastasis suppression by chromosome 6: Evidence for a pathway regulated by CRSP3 and TXNIP. *Cancer Res* 63: 432–440, 2003.
12. Grodstein F, Speizer F, and Hunter D. A prospective study of incident squamous cell carcinoma of the skin in the nurses' health study. *J Natl Cancer Inst* 87: 1061–1066, 1995.
13. Halliwell B and Gutteridge JMC. *Free radicals in biology and medicine*. Oxford: Clarendon Press, 1999, p 58.
14. Han S, Jeon J, Ju H, Jung U, Kim K, Yoo H, Lee Y, Song K, Hwang H, Na Y, Yang Y, Lee K, and Choi I. VDUP1 upregulated by TGF-b1 and 1,25-dihydorxyvitamin D_3 inhibits tumor cell growth by blocking cell-cycle progression. *Oncogene* 22: 4035–4046, 2003.
15. Hirai F, Motoori S, Kakinuma S, Tomita K, Indo H, Kato H, Yamaguchi T, Yen H, St. Clair D, Nagano T, Ozawa T, Saisho H, and Majima H. Mitochondrial signal lacking manganese superoxide dismutase failed to prevent cell death by reoxygenation following hypoxia in a human pancreatic cancer cell line, KP4. *Antioxid Redox Signal* 6: 523–535, 2004.
16. Hiroyasu M, Ozeki M, Kohda H, Echizenya M, Tanaka T, Hiai H, and Toyokuni S. Specific allelic loss of *$p16^{INK4A}$* tumor suppressor gene after weeks of iron-mediated oxidative damage during rat renal carcinogenesis. *Am J Pathol* 160: 419–424, 2002.
17. Hodgson J and Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Ann Occup Hyg* 44: 565–601, 2000.

18. Hui T, Sheth S, Diffley J, Potter D, Lusis A, Attie A, and Davis R. Mice lacking thioredoxin interacting protein provide evidence linking cellular redox state to appropriate response to nutritional signals. *J Biol Chem* 279: 24387–24393, 2004.
19. Ikarashi M, Takahashi Y, Ishii Y, Nagata T, Asai S, and Ishikawa K. Vitamin D_3 up-regulated protein 1 (VDUP1) expression in gastrointestinal cancer and its relation to stage of disease. *Anticancer Res* 22: 4045–4048, 2002.
20. Iuchi K, Aozasa K, Yamamoto S, Mori T, Tajima K, Minato K, Mukai K, Komatsu H, Tagaki T, and Kobashi Y. Non-Hodgkin's lymphoma of the pleural cavity developing from long-standing pyothorax: summary of clinical and pathological findings in thirty-seven cases. *Jpn J Clin Oncol* 19: 249–257, 1989.
21. Joensuu H. Treatment of inoperable gastrointestinal stromal tumor (GIST) with imatinib (Glivec, Gleevec). *Med Klin (Munich)* 97(suppl 1): 28–30, 2002.
22. Kamijo T, Weber JD, Zambetti G, Zindy F, Roussel MF, and Sherr CJ. Functional and physical interactions of the ARF tumor suppressor with p53 and Mdm2. *Proc Natl Acad Sci U S A* 95: 8292–8297, 1998.
23. Kim A, Zhong W, and Oberley T. Reversible modulation of cell cycle kinetics in NIH/3T3 mouse fibroblasts by inducible overexpression of mitochondrial manganese superoxide dismutase. *Antioxid Redox Signal* 6: 489–500, 2004.
24. Kitano H. Cancer as a robust system: Implications for anticancer therapy. *Nat Rev Cancer* 4: 227–235, 2004.
25. Loeb LA. Mutator phenotype may be required for multistage carcinogenesis. *Cancer Res* 51: 3075–3079, 1991.
26. Nishigori C, Hattori Y, and Toyokuni S. Role of reactive oxygen species in skin carcinogenesis. *Antioxid Redox Signal* 6: 561–570, 2004.
27. Nishinaka Y, Nishiyama A, Masutani H, Oka S, Ahsan K, Nakayama Y, Ishii Y, Nakamura H, Maeda M, and Yodoi J. Loss of thioredoxin-binding protein-2/vitamin D_3 up-regulated protein 1 in human T-cell leukemia virus type I-dependent T-cell transformation: Implications for adult T-cell leukemia leukemogenesis. *Cancer Res* 64: 1287–1292, 2004.
28. Nishiyama A, Matsui M, Iwata S, Hirota K, Masutani H, Nakamura H, Takagi Y, Sono H, Gon Y, and Yodoi J. Identification of thioredoxin-binding protein-2/vitamin D_3 up-regulated protein 1 as a negative regulator of thioredoxin function and expression. *J Biol Chem* 274: 21645–21650, 1999.
29. Nishiyama Y, Suwa H, Okamoto K, Fukumoto M, Hiai H, and Toyokuni S. Low incidence of point mutations in *H-, K-* and *N-ras* oncogenes and *p53* tumor suppressor gene in renal cell carcinoma and peritoneal mesothelioma of Wistar rats induced by ferric nitrilotriacetate. *Jpn J* Cancer Res 86: 1150–1158, 1995.
30. Oberley L. Anticancer therapy by overexpression of superoxide dismutase. *Antioxid Redox Signal* 3: 461–472, 2001.
31. Oberley T. Mitochondria, manganese superoxide dismutase , and cancer. *Antiox Redox Signal* 6: 483–487, 2004.
32. Oberley T, Xue Y, Zhao Y, Kiningham K, Szweda L, and St. Clair D. In situ reduction of oxidative damage, increased cell turnover, and delay of mitochondrial injury by overexpression of manganese superoxide dismutase in a multistage skin carcinogenesis model. *Antioxid Redox Signal* 6: 537–548, 2004.
33. Ohshima H, Tatemichi M, and Sawa T. Chemical basis of inflammation-induced carcinogenesis. *Arch Biochem Biophys* 417: 3–11, 2003.
34. Oikawa S and Kawanishi S. Site-specific DNA damage at GGG sequence by oxidative stress may accelerate telomere shortening. *FEBS Lett* 453: 365–368, 1999.
35. Oka S, Liu W, Masutani H, Hirata H, Shinkai Y, Yamada S, Yoshida T, Nakamura H, and Yodoi J. Impaired fatty acid utilization in thioredoxin binding protein-2 (TBP-2)-deficient mice: A unique animal model of Reye syndrome. *FASEB J* 20: 121–123, 2006.
36. Pani G, Colavitti R, Bedogni B, Fusco S, Ferraro D, Borrello S, and Galeotti T. Mitochondrial superoxide dismutase: A promising target for new anticancer therapies. *Curr Med Chem* 11: 1299–1308, 2004.
37. Park S, Kim W, Choi U, Han S, Kim Y, Kim Y, Chung M, Nam K, Kim D, Cho S, and Hahm K. Amelioration of oxidative stress with ensuing inflammation contributes to chemoprevention of H. pylori-associated gastric carcinogenesis. *Antioxid Redox Signal* 6: 549–560, 2004.
38. Preston D, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, Kamada N, Dohy H, Matsuo T, and T M. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950–1987. *Radiat Res* 137: S68–S97, 1994.
39. Ridnour L, Oberley T, and Oberley L. Tumor suppressive effects of MnSOD overexpression may involve imbalance in peroxide generation versus peroxide removal. *Antioxid Redox Signal* 6: 501–512, 2004.
40. Sen C and Packer L. Antioxidant and redox regulation of gene transcription. *FASEB J* 10: 709–720, 1996.
41. Siddiqui I, Afaq F, Adhami V, Ahmad N, and Mukhtar H. Antioxidants of the beverage tea in promotion of human health. *Antioxid Redox Signal* 6: 571–582, 2004.
42. Slamon D, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, and Norton L. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 344: 783–792, 2001.
43. Steenken S. Purine bases, nucleosides, and nucleotides: Aqueous solution redox chemistry and transformation reactions of their radical reactions and e^- and $\cdot OH$ adducts. *Chem Rev* 89: 503–520, 1989.
44. Steinmetz K and Potter J. Vegetables, fruit, and cancer prevention: A review. *J Am Diet Assoc* 96: 1027–1039, 1996.
45. Sugimura T. Multistep carcinogenesis: a 1992 perspective. *Science* 258: 603–607, 1992.
46. Tanaka T, Iwasa Y, Kondo S, Hiai H, and Toyokuni S. High incidence of allelic loss on chromosome 5 and inactivation of *p15 INK4B* and *p16 INK4A* tumor suppressor genes in oxystress-induced renal cell carcinoma of rats. *Oncogene* 18: 3793–3797, 1999.
47. Toyokuni S. Reactive oxygen species-induced molecular damage and its application in pathology. *Pathol Int* 49: 91–102, 1999.

48. Toyokuni S, Akatsuka S, Aung TT, and Dutta KK. Free radical-induced carcinogenesis: target genes and fragile genome sites. *Free Radic Res* 39 (suppl 1): S30, 2005.
49. Uchida K. 4-Hydroxy-2-nonenal: A product and mediator of oxidative stress. *Prog Lipid Res* 42: 318–343, 2003.
50. Vogelstein B and Kinzler KW. *The genetic basis of human cancer*. New York: McGraw-Hill, 1998.
51. von Zglinicki T, Pilger R, and Sitte N. Accumulation of single-strand breaks is the major cause of telomere shortening in human fibroblasts. *Free Radic Biol Med* 28: 64–74, 2000.
52. Zhong W, Yan T, Webber M, and Oberley T. Alteration of cellular phenotype and responses to oxidative stress by manganese superoxide dismutase and a superoxide dismutase mimic in RWPE-2 human prostate adenocarcinoma cells. *Antioxid Redox Signal* 6: 513–522, 2004.

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2. Ah-Mee Park, Masatoshi Kudo, Satoru Hagiwara, Masaki Tabuchi, Tomohiro Watanabe, Hiroshi Munakata, Toshiharu Sakurai. 2012. p38MAPK suppresses chronic pancreatitis by regulating HSP27 and BAD expression. *Free Radical Biology and Medicine* **52**:11-12, 2284-2291. [CrossRef]
3. Helen E. Townley, Elizabeth Rapa, Gareth Wakefield, Peter J. Dobson. 2012. Nanoparticle augmented radiation treatment decreases cancer cell proliferation. *Nanomedicine: Nanotechnology, Biology and Medicine* **8**:4, 526-536. [CrossRef]
4. Yeung Bae Jin, Ga-Young Kang, Jae Seon Lee, Jong-Il Choi, Ju-Woon Lee, Seung-Cheol Hong, Sung Ho Myung, Yun-Sil Lee. 2012. Effects on micronuclei formation of 60-Hz electromagnetic field exposure with ionizing radiation, hydrogen peroxide, or c-Myc overexpression. *International Journal of Radiation Biology* 1-7. [CrossRef]
5. Helen E. Townley, Jeewon Kim, Peter J. Dobson. 2012. In vivo demonstration of enhanced radiotherapy using rare earth doped titania nanoparticles. *Nanoscale* **4**:16, 5043. [CrossRef]
6. Lian Shu Piao, Wonhee Hur, Taek-Kyun Kim, Sung Woo Hong, Sung Woo Kim, Jung Eun Choi, Pil Soo Sung, Myeong Joon Song, Byeong-Chel Lee, Daehee Hwang, Seung Kew Yoon. 2011. CD133+ liver cancer stem cells modulate radioresistance in human hepatocellular carcinoma. *Cancer Letters* . [CrossRef]
7. Christopher Runchel , Atsushi Matsuzawa , Hidenori Ichijo . 2011. Mitogen-Activated Protein Kinases in Mammalian Oxidative Stress Responses. *Antioxidants & Redox Signaling* **15**:1, 205-218. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
8. James E. Klaunig, Zemin Wang, Xinzhu Pu, Shaoyu Zhou. 2011. Oxidative stress and oxidative damage in chemical carcinogenesis. *Toxicology and Applied Pharmacology* **254**:2, 86-99. [CrossRef]
9. Christine Lehner , Renate Gehwolf , Herbert Tempfer , Istvan Krizbai , Bernhard Hennig , Hans-Christian Bauer , Hannelore Bauer . Oxidative Stress and Blood–Brain Barrier Dysfunction Under Particular Consideration of Matrix Metalloproteinases. *Antioxidants & Redox Signaling*, ahead of print. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
10. Liang Hu, Lei Chen, GuangZhen Yang, Liang Li, HanYong Sun, YanXin Chang, QianQian Tu, MengChao Wu, HongYang Wang. 2011. HBx Sensitizes Cells to Oxidative Stress-induced Apoptosis by Accelerating the Loss of Mcl-1 Protein via Caspase-3 Cascade. *Molecular Cancer* **10**:1, 43. [CrossRef]
11. Guanwu Li, Lai Sheung Lee, Muyao Li, Sai Wah Tsao, Jen-Fu Chiu. 2011. Molecular changes during arsenic-induced cell transformation. *Journal of Cellular Physiology* n/a-n/a. [CrossRef]
12. Xinjian Peng, Avani Vaishnav, Genoveva Murillo, Fatouma Alimirah, Karen E.O. Torres, Rajendra G. Mehta. 2010. Protection against cellular stress by 25-hydroxyvitamin D3 in breast epithelial cells. *Journal of Cellular Biochemistry* **110**:6, 1324-1333. [CrossRef]
13. Yao Liu, Huanjun Huang, Jusheng Lin, Qiang Zhang, Jinquan Tan, Jinghua Ren. 2009. Suppressive effects of genomic imprinted gene PEG10 on hydrogen peroxide-induced apoptosis in L02 cells. *Journal of Huazhong University of Science and Technology [Medical Sciences]* **29**:6, 705-709. [CrossRef]
14. Dunyaporn Trachootham, Jerome Alexandre, Peng Huang. 2009. Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach?. *Nature Reviews Drug Discovery* **8**:7, 579-591. [CrossRef]
15. E Giannoni, T Fiaschi, G Ramponi, P Chiarugi. 2009. Redox regulation of anoikis resistance of metastatic prostate cancer cells: key role for Src and EGFR-mediated pro-survival signals. *Oncogene* **28**:20, 2074-2086. [CrossRef]
16. N TOBAR, M CACERES, J SANTIBANEZ, P SMITH, J MARTINEZ. 2008. RAC1 activity and intracellular ROS modulate the migratory potential of MCF-7 cells through a NADPH oxidase and NF#B-dependent mechanism. *Cancer Letters* **267**:1, 125-132. [CrossRef]
17. Toshiharu Sakurai, Guobin He, Atsushi Matsuzawa, Guann-Yi Yu, Shin Maeda, Gary Hardiman, Michael Karin. 2008. Hepatocyte Necrosis Induced by Oxidative Stress and IL-1# Release Mediate Carcinogen-Induced Compensatory Proliferation and Liver Tumorigenesis. *Cancer Cell* **14**:2, 156-165. [CrossRef]
18. Dimitrios Galaris, Vasiliki Skiada, Alexandra Barbouti. 2008. Redox signaling and cancer: The role of “labile” iron. *Cancer Letters* **266**:1, 21-29. [CrossRef]
19. Mario E. Goetz, Andreas Luch. 2008. Reactive species: A cell damaging rout assisting to chemical carcinogens. *Cancer Letters* **266**:1, 73-83. [CrossRef]

20. Fabio Farinati, Romilda Cardin, Mauro Cassaro, Marina Bortolami, Donato Nitti, Chiara Tieppo, Giovanni Zaninotto, Massimo Rugge. 2008. Helicobacter pylori, inflammation, oxidative damage and gastric cancer: a morphological, biological and molecular pathway. *European Journal of Cancer Prevention* **17**:3, 195-200. [CrossRef]
21. P Sacca, R Meiss, G Casas, O Mazza, J C Calvo, N Navone, E Vazquez. 2007. Nuclear translocation of haeme oxygenase-1 is associated to prostate cancer. *British Journal of Cancer* **97**:12, 1683-1689. [CrossRef]
22. Ju Hee Lim, Hae-Suk Park, Jung-Kap Choi, Ik-Soo Lee, Hyun Jin Choi. 2007. Isoorientin induces Nrf2 pathway-driven antioxidant response through phosphatidylinositol 3-kinase signaling. *Archives of Pharmacal Research* **30**:12, 1590-1598. [CrossRef]
23. Marcus S. Cooke, Joy E. Osborne, Rajinder Singh, Vilas Mistry, Peter B. Farmer, Mark D. Evans, Peter E. Hutchinson. 2007. Evidence that oxidative stress is a risk factor for the development of squamous cell carcinoma in renal transplant patients. *Free Radical Biology and Medicine* **43**:9, 1328-1334. [CrossRef]
24. Arthur Hilliker, Kim Disher, Adonis Skandalis. 2007. Evidence of the modulation of mRNA splicing fidelity in humans by oxidative stress and p53. *Genome* **50**:10, 946-953. [CrossRef]
25. Ignacio Dolado, Aneta Swat, Nuria Ajenjo, Gabriella De Vita, Ana Cuadrado, Angel R. Nebreda. 2007. p38# MAP Kinase as a Sensor of Reactive Oxygen Species in Tumorigenesis. *Cancer Cell* **11**:2, 191-205. [CrossRef]