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RESEARCH ARTICLE

THE p53 GENE DEMYSTIFIED -REVEALING SOME TRUTHS ABOUT THE p53'S BEHAVIOR AND WHY IT MUTATES LEADING TO CANCER GENESIS

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ABSTRACT

It is known that within normal cells, genetic mutations don't occur and normal cells don't develop into cancer cells, but within abnormal cells if genetic mutations do develop, the p53 tumor protein should normally monitor this and guard the body from these dangerous cells developing or being replicated – like with cancerogenesis and tumorigenesis. This tumor protein known as the "guardian of the genome" or "cell cycle police" is normally extremely sensitive to cellular abnormalities - its true job is to protect the integrity, genetic growth and development of future daughter cells, thus protecting cellular development in the body overall. Policing, securing and preventing cells from carrying on dangerous genetic mutations with "cell-cycle arrest" and "induced apoptosis" is vitally the most important role of the normal p53 - but just as fraud and corruption is a regular occurrence with authority, these "gene police" can also mutate and become corrupt, immoral and start helping cancer cells progress instead of stopping them. When the p53 starts allowing cell mutation and supporting abnormal cell development this contradictory, reprehensible behavior becomes an obviously incriminating focal point within the genetic "cancer equation" for researchers to question. Asking why and how this change occurs is relevant because this specific moment is connected to "cancer's start-up." Detailing this occurrence and all of the pathomechanisms involved in this "switch of the p53" needs to occur so that it can be stopped! Just like with any form of fraud or corruption, exposing and elucidating this inconspicuous shrouded "moment" and identifying all causative factors involved is necessary but difficult for cancer researchers. Due to the striking similarities of this situation to interrogating a corrupt official – this issue similarly needs a non-biased "internal affairs" type of investigation – to dig down deep and bring out all relevant factors into the light. So far, this p53 investigation has been labeled as "difficult to understand" or as "having an unknown cause" but with honest appraisal, the true cause can be identified. Therefore, this article is about exposing the cause of the p53's switch, examining the p53 from different perspectives and going beyond any traditionally occluded views to find the truth. The benefits of this interrogation will help in the development of new p53 based cancer treatments.

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INTRODUCTION

The p53 is actually a very important tumor suppressing protein located on the 17th chromosome.[1] It is the gene involved in policing and regulating the cell's cycles before DNA replication and cell division, making it responsible for controlling tumor suppression and halting cell mitosis in cells that have sustained DNA damage; this is why it is known as the "guardian of the genome."[2 3] However, when it is defective, the genetic encoding in the p53 is mutated and the "mutant p53's" behavior switches from guarding to facilitating the cancer pathomechanism instead.[4] In fact, 50% of all human tumors contain mutant p53 proteins, while contrastingly - normal cells only contain very low levels of normal p53 proteins.[5] Once mutant the p53 continues to behave inappropriately, allowing damaged cells to replicate and divide it starts facilitating oncogenic mutations and cancer development.[6] The fact that this p53 protein mutates more than all of the other 20,000 human genes is shocking.[7] Why this

[1] Primary Information of p53 gene
www.bioinformatics.org/p53/intorduction.html
[2] Primary Information of p53 gene
www.bioinformatics.org/p53/intorduction.html
[3] Wiley, Strachan and Read, The p53 Human Molecular Genetics 4
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[4] Wiley, Strachan and Read, The p53 Human Molecular Genetics 4
www.wiley.com/legacy/products/subject/life/strachan/strafigs/index.htm 1999
[5] Primary information of the p53 gene
www.bioinfomatics.org/p53/introduction.html
[6] Effects of Oxidation and Inflammation, Cancer, Prostate Cancer
www.natap.org/2009/HIV/052109_01.htm
[7] Role of p53 in the Cell Cycle hhmi BioInteractive Data Point Education

happens is a question that has been asked many times and is considered mysterious and unknown, but there *is* a reason behind this scandalous transformation and this information is needed for developing better methods in preventing and treating cancer on the molecular, genetic and cellular levels.

Backgrounds

The p53 has been widely studied in the past few decades due to suspicions of it's behavior of being a "traitor" and contrarily playing a direct role in promoting cancer and tumor genesis by being an accomplice in excess cell death and provoking enhanced cell survival. Detailed observation shows that the p53 *is* involved, and works by using transcription factors to mismanage cell response and unleashing an assortment of stress factors through complex signaling networks. How it does this is by sabotaging normal cells so after they endure a variety of harsh conditions including things like DNA damage, hypoxia and oxidative stress the p53 also becomes modified and no longer protects. This p53 change empowers it with new stability that allows it to move into the cell's nucleus, where it can activate the expression of specific genes that can either provoke cell cycle regulation, DNA repair, senescence or cause cell death.[8] Researchers found that along with the p53's change, the metabolism in cancer cells is also altered and this is due to the Warburg effect.[9] These metabolic alterations determine exactly how cells respond to changes in nutrient and oxygen supplies to promote cell proliferation, growth and survival. Therefore, there are many factors involved.

Research and studies have uncovered only a percentage of the identifiable influences impacting the p53 leading it into problems, wanting to know more like exactly what plays a pivotal role in this metabolic shift of the p53 is still at large.[10] Within this study, all aspects will be truthfully investigated in hope of attaining a broader exposure on the cause.

With the ultimate goal of better cancer treatment designs based on p53 function being the prime motivator – a main hope is the possibility of being able to reinstate the p53's policing actions. First, more proof is still needed for total exposure of waylaid functions, and the process of gathering this concrete evidence is still underway. Here we will reveal the key causatives factors in a 3 phase breakdown showing through diagrams, the mechanisms behind the p53's switch. Since it has already been scientifically identified that p53s do switch, mutate and then promote and support genetic mutation we will go beyond that in this review to break down "why" in this mystery of the p53.[11]

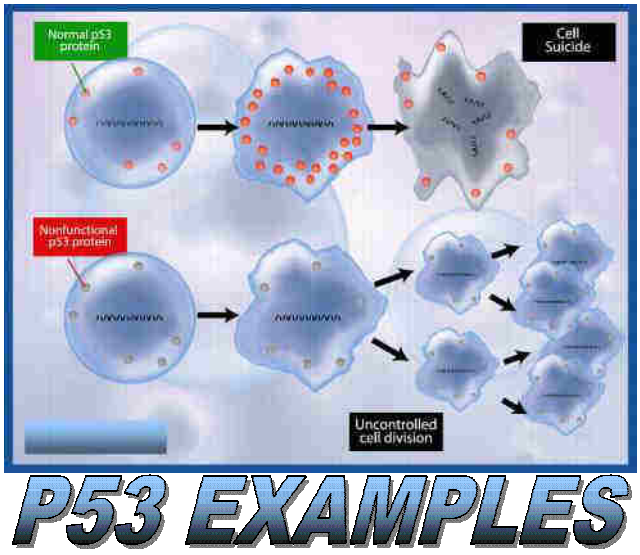

Figure 1. p53 mutation illustrated

Epigenetics explained

This overview of the p53 mutation will begin with "epigenetic factors" and their many negative causative influences impacting our health. Surprisingly these factors are a main part of our normal day-to-day lifestyles. [12] With these epigenetic factors leading so many to succumbing to disease it provokes the question of the moral issues behind what we are doing to ourselves as a society that is leading us straight to illness. [13] We need to start facing the facts of what we are bringing on ourselves in terms of disease causation.[14] In fact, identifying what disease causing factors are avoidable and which are not – especially in terms of cancer genesis is important. Also, revealing how the p53 being continually impacted by epigenetic factors is important, but how aware of this is the general population? One professor of Biological Sciences in Australia at the University of Queensland wrote the book "It Takes A Genome: How a Clash Between Our Genes and Modern Life Is Making Us Sick," in his book he suggests that "The increased rates of diseases such as diabetes, cancer and Alzheimer's are due to human genes being unable to cope with the 21st century Western lifestyle.' [15] He continues on to say that "In the last two generations or so, we've changed our environment so much in terms of what we eat, what pathogens we are exposed to and the stresses we put on ourselves psychologically." "The rapid cultural change means our genes are no longer in a comfort zone –that this has pushed us outside of the realm that the genome can normally tolerate, and that because of that we've gone from being 1% susceptible to these diseases to more like 10-15%."[16]

Materials p53 PDF Biology of Cells www.bioInteractive.org Published December 2017

[8] Xing-ding Zhang, Zheng-Hong Qin and JinWang, APS Acta Pharmacologica Sinica 2010 Sept 31(9): 1208-1212 The role of p53 in cell metabolism PMCID:PMC4002322 PMID:20729871 www.ncib.nln.nih.gov/pmc/articles/PMC4002322/

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[11] p53 mutations in Cancer WRITTEN BY Muller PA, vousden KH, Nat cell boil. 2013 Jan;15(1): 2-8 www.ncbi.nlm.nih.gov/pubmed/23263379

[12] UQ RESEARCH FINDS OUR lifestyle is making us sick WRITTEN BY Professor Gibbson from UQ's school of Biology 2-2009 www.uq.edu.au/news/article/2009/02/uq-research-finds-our-lifestyle-making-us-sick

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[16] UQ RESEARCH FINDS OUR lifestyle is making us sick WRITTEN BY

The connection here is through the genes being attacked and influenced by what are known as epigenetic factors - which is causing oxidative stress. As a gene, the p53 is clearly very susceptible to this stress.[17] Now that we know about epigenetic factors overwhelming our genes, we need to know more details about how they impact the p53 gene. It is when the various negative epigenetic factors combine and accumulate they create oxidative stress so intense that it instigates a cascade of events that leads to genetic instability which promotes the switch within the coding of genes including the p53. [18] This switch in coding leads to gene mutation which disables the p53's guardian powers, subsequently allowing cellular division to go awry – permitting healthy cells to mutate into cancer cells. [19] It's broader research like this that reveals that the mutation of the p53 is brought on not only by things we cannot see with the naked eye on the molecular level, but with things we *can* see on the macroscopic levels in our lifestyles. Our lifestyles are implicitly linked to generating overwhelming oxidative stress that leads to the genetic instability causing the p53 to mutate. Looking deeper and verifying these details then mapping the exact steps beginning from the normal p53 – and ending with the cancer supporting mutant p53 will now be done in hope that from a clever and honest viewpoint this information will serve a grander purpose to support the design of new p53 based treatments.

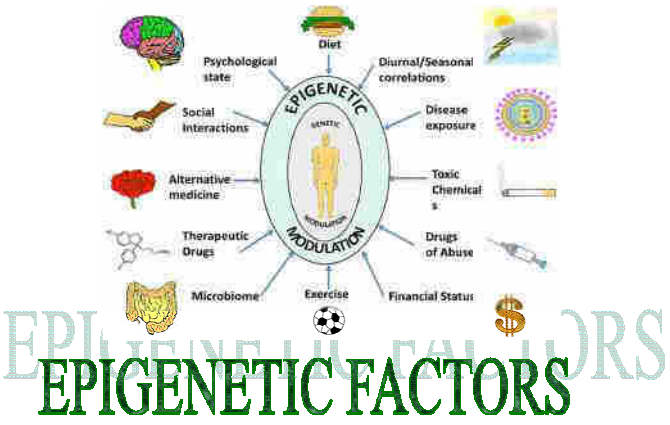

Figure 4. Epigenetic factors illustrated

This illustration shows just a few of the epigenetic factors we encounter

Epigenetics further explained

Epigenetic factors are actually a variety of influences around and within us that affect us all. [20] The term itself "epigenetics" actually refers to what is superlative to the genetic aspects of our physicality, and literally "upon our genes." In fact, the Greek prefix "epi" implies features that are "on top of" or "in addition to" our genes. The scientific field of epigenetics was actually developed in 1940's by Conrad Waddington out of necessity due to the vast increasing amounts of epigenetic influences involved in our day-to-day existence. Epigenetics is the technical study of what impacts gene mechanisms within the molecule, DNA/RNA function and replication as well as their systems of inheritance of other traits and it is linked to p53 function and mutation.[21] Epigenetic study looks directly at the factors that switch genes "on and off" and how cells read genes or eventually no longer respond to alterations in the actual DNA sequence. [22] In 2006 alone, over 2500 articles on this topic were published and by 2010, 13,000 and by 2013 the number still increased to 17,000 with as many as 45 new documents being written per day making this a very popular field of study.[23] Dedicated to making detailed observations on how epigenetic factors are connected to the vast array of new illnesses linked to external and environmental factor causation this field is necessary.[24] Epigenetic analysis will continue to denote all changes that affect gene activity and expression and also describe heritable phenotypic change resulting from external and environmental factors ultimately influence genetic behaviors.[25] Epigenetics are important and central to this review topic because the oxidative damage they induce is the strongest element negatively impacting the p53, during cancer start-up.[26]

This start-up also called "cancer genesis" is defined as the formation of cancer by uncontrolled multiplication of cells but this process can only begin after genetic adaptation and mutation of the p53's occurs. [27] Coincidently cell mutation is heavily intertwined with p53 mutation as both are impacted by the same negative external and environmental stimuli, these negative stimuli *are* the same epigenetic influences. [28] Primarily responsible for "turning off" the p53 epigenetic influences lead it to stop functioning as a guardian while simultaneously also negatively impacting normal cells, causing them to mutate, once this occurs, the following cascade of negative events of both normal cells and p53s mutating and promoting cancer genesis together occurs.[29] Figure 5 above shows just a few of the main epigenetic factors that have the power to overthrow normal cellular and genetic function and it is obvious that they are a normal part of the human lifestyle. Unfortunately these epigenetic influences actually cause the numbers of p53 proteins to increase - but the numbers of p53s actually need to stay low because high levels of normal p53s are dangerous and accelerate the aging process with excessive apoptosis occurring.[30] Epigenetic factors include things like chemicals and poisons found in our environment, cigarette smoke, alcohol, drugs, car pollution, unhealthy processed junk foods, GMOs, radiation... this is just the short list.[31] Continual

Professor Gibbson from UQ's school of Biology 2-2009 www.uq.edu.au/news/article/2009/02/uq-research-finds-our-lifestyle-making-us-sick

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[18] Epigenetic modifications and human disease Written by Portela A, Esteller M www.ncbi.nlm.nih.gov/pubmed/20944598

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[23] GENETICS 2015 apr, 199(4) 887-896 What do You Mean, "Epigenetic"? Carrie Deans. Keith A. Maggert www.ncbi.nlm.nih.gov/pmc/articles/PMC4391566/

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[30] The truth about cancerthetruthaboutcancer.com/zinc-deficiency-cancer/

[31] Epigenetic factors that influence the oxidative stress in cells

exposure to these factors creates oxidative stress in the body which is problematic. [32] Processed sugar is specifically a problem because it feeds and supports bacteria present in inflammation which is directly linked to cancer genesis as well and sugar consumption results in oxidative stress caused by the subsequent acid ph and this supports inflammation problems. [33] So overall, Epigenetic factors and oxidative stress are directly linked to the p53's dysfunction - epigenetic induced oxidative stress is linked directly to cancer genesis because it causes normal cells to mutate and transform in a step-by-step process labeled as "oxidative stress gene mutation" which turns them into cancer cells.[34] Unfortunately, all oxidative damage even worsens with age because free radicals accumulate and cause more disease on the cellular, genetic and epigenetic levels, especially causing abnormal cell division that is associated with cancer.[35] This explains why the rate of cancer occurrence increases with age. [36] This also explains how age-amplified oxidative stress is instrumental in impacting gene and cell function. Research shows that the majority of all DNA mutations bear the signature of oxidative stress as their cause.[37]

From epigenetic influences we get oxidative stress which causes free radicals – let's see how they impact the geneome

The connection starts with Epigenetic factors which cause oxidative stress and then oxidative stress creates free radicals also called Rapid Oxygen Species (ROS) or (RNS). On the microscopic level free radical damage can been seen in unstable molecules that behave radically as they steal ionic charges from balanced cells to rebalance themselves, free radicals behaving aggressively this way generate molecular damage and genetic instability.[38]

Normally these free radicals should be quickly eliminated by protective antioxidants within, but when they are not, it is then that cancer's initiation and progression is supported. [39] The specific imbalance between free radicals and the body's ability to recover with detoxification by antioxidants is what leads to genetic damages and subsequential physiological stress within the cell's genome, this genetic instability weakens gene function, and that it when it becomes difficult for the p53 to do its job which should be to put the brakes on tumor development.[40]

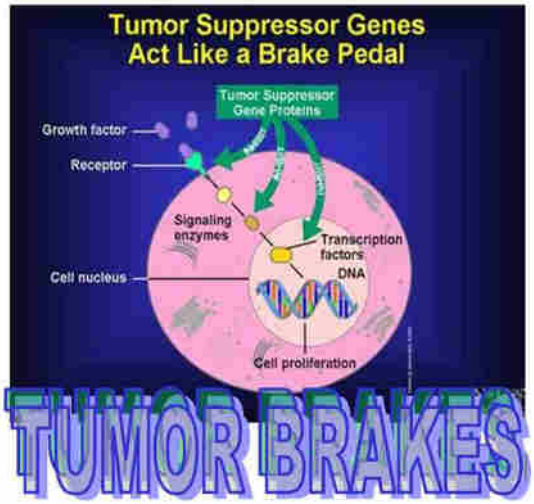

Figure 5: The p53 Tumor Brakes

Tumor suppression is like putting the brakes on

To prevent free radical damage, the imbalance between the production and disposal of (ROS) and (RNS) needs to be meticulously maintained, because if not subsequent p53 mutation and cancer genesis can occur because it is connected directly to the accumulation of both.[41] This is because (ROS) and (RNS) oxidative stress have protumorigenic effects such as increasing DNA mutation rates, inducing DNA damage, causing genome instability which in turn allow for tumorigenic cell proliferation.[42] The subsequent damage causes a mixture of damaged biomolecules, cells and genes including the p53 – plus overall negative impact on the entire body's physiological function.[43]

Oxidative stress, inflammation, & The p53

Epigenetic induced oxidative stress is also directly linked to chronic inflammation which is a pathomechanism well known to be present in the startup of cancer.[44] Inflammation facilitates cancer by activation of a variety of transcription factors including NF-Kb, AP-1, p53, HIF2a, PPAR-y, B-catenin/Wnt, and Nrf2.[45] This activation leads to the expression of over 500 different genes including growth factors, inflammatory cytokines, cell cycle regulatory molecules and anti-inflammatory molecules - causing serious problems for cells. [46] Identifying the links here between oxidative stress, chronic

[32] Epigenetic factors that influence the oxidative stress in cells
[33] Epigenetic factors that influence the oxidative stress in cells
[34] Oxidative Stress is Underlying cause of Huge Numbers Of genetic Mutations Study Finds www.sciencedaily.com/releases/2009/09/090907162318.htm Written by Oregon State University 2009
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inflammation, the p53's mutation and cancer genesis is imperative in demystifying the p53's negative behavior. Mapping these connections helps to illustrate mutation as a cascade. It occurs as follows, epigenetic factors cause oxidative stress which leads to free radical damage, causing inflammation and the activation of inflammatory pathways which lead to genetic instability that mutates gene encoding, with improper gene encoding the p53 mutates and then allows normal cells to mutate into tumor cells without stopping cell cycles or inducing apoptosis as it should. [47] The tumor cell's survival, proliferation, invasive abilities, angiogenesis and stem cell survival are also all supported by oxidative stress.[48] Research even shows that oxidative stress, chronic inflammation and cancer are always seen occurring together as a trio,[49] the p53's mutation initiation is also directly involved.[50]

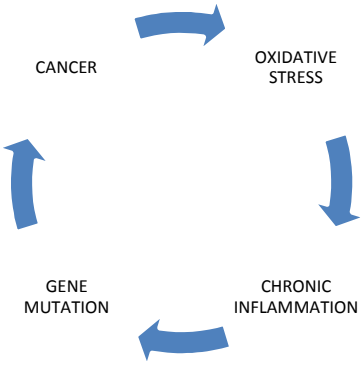
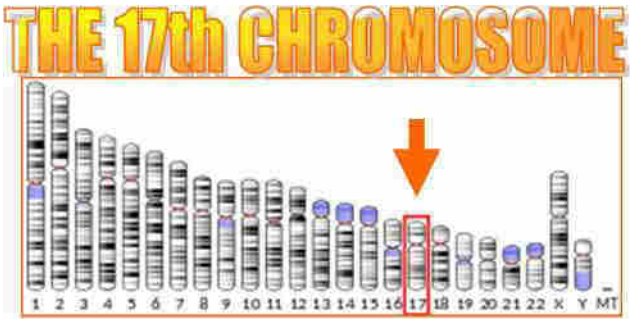


Figure 6. The trio – oxidative stress, chronic inflammation and gene mutation leading to cancer

Scientific Investigators even reveal that they find inflammatory cells inside of most cancer tissue that is removed surgically and that during surgery they can see chronic inflammation in the area leads to wasting of normal tissue and tissue atrophy – this all occurs directly near precancerous and cancerous tissue within the tumor microenvironments.[51]



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Details of DNA damage – guanine and 17p13.1 THE P53 locus deletion and mutation

Studies show that DNA damage caused by stress is one of the primary instigators of the mutation process that leads to aging, cancer and other diseases.[52] Since the p53 mutation is caused by this DNA damage, it is the common event most frequently identified in human cancers. More specifically the deactivation of the p53 is caused by several distinct mechanisms like point mutation, chromosome deletion, degradation by up-regulation of MDM2 and even by abnormal splicing. The p53 mutation does differ by the type of tumor involved for example it has been shown that in 70% of lung cancers and 60% in colon cancers the p53 locus was deleted or inactivated.[53] [54] Experts that study genetic mutation, state that this type of damage very rarely occurs unless it is induced by something - like oxidation.[55] The instilled protective functions of the p53 are not strong enough to guard against a continual onslaught of oxidative stress because of the fact that oxidative induced genetic changes directly impact Guanine.

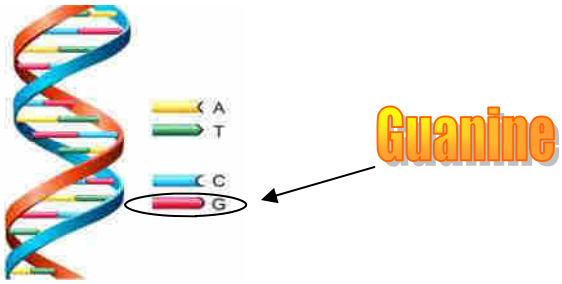

Figure 7. DNA damage targets guanine in the dna

Guanine is one of the genetic nucleotides that make up the DNA structure; it is especially sensitive to oxidative damage and oxidizes more easily, it is insoluble to water but soluble in dilute acids and bases. [56] Guanine forms nucleotide derivatives that perform important functions in cellular metabolism, and it is found that mutant p53s induce the GEF-H1 oncogenes to exchange, resulting in accelerated cell proliferation in tumor cells.[57] Mutant p53 cells even provide tumor cells with certain gainful properties like accelerated cell proliferation, increased

[52] Oxidative Stress is Underlying cause of Huge Numbers Of genetic Mutations Study Finds www.sciencedaily.com/releases/2009/09/090907162318.htm Written by Oregon State University 2009

[53] CANCER RESEARCH Mutant p53 Induces the GEF-H1Oncogene, a Guanine Nucleotide Exchange Factor-H1 for RhoA, Resulting in Accelerated Cell Proliferation in Tumor Cells Shinji Mizuarai, Kazunori Yamanaka and Hidehito Kotani DOI: 10.1158/0008-5472.CAN-05-4629Publisher June 2006 www.cancerres.aacrjournals.org/content/66/12/6319

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[56] Oxidative Stress is Underlying cause of Huge Numbers Of genetic Mutations Study Finds www.sciencedaily.com/releases/2009/09/090907162318.htm Written by Oregon State University 2009

[57] CANCER RESEARCH Mutant p53 Induces the GEF-H1Oncogene, a Guanine Nucleotide Exchange Factor-H1 for RhoA, Resulting in Accelerated Cell Proliferation in Tumor Cells Shinji Mizuarai, Kazunori Yamanaka and Hidehito Kotani DOI: 10.1158/0008-5472.CAN-05-4629Publisher June 2006 www.cancerres.aacrjournals.org/content/66/12/6319

metastasis and resistance to apoptosis. It's due to an exchange through transcription of guanine based elements the p53 is found to switch. When studied it is found that the GEF-H1 expression is significantly instigated by mutant p53s. These GEF-H1 expression levels directly correlate to the p53's status of mutation, so the more GEF-H1 contributes to tumor progression is associated with more p53 mutation - this was found in 32 cancer cell lines in a study done.[58] Another cause of DNA damage is cellular oxygen deprivation which is caused by anoxia and hypoxia which is the absence of or low levels of oxygen respectively, and being deprived of adequate oxygen supply whether in the whole body or a specific tissue area triggers a pathological response.[59] This is because normal cells and tissue are both metabolically dependant on oxygen to produce energy, so oxygen deprivation and inefficiencies prohibit proper metabolic function which leads to free-radical damage and causes oxidative damages to proteins, fats and especially DNA.[60] While the p53 switch may be mysterious after this amount of revelation, it is clear that epigenetic factors are the negative influencers that lead to oxidative stress which starts the negative cascade of damage which derails p53 function.[61]

There are more details about the p53's mutation and cancerogenesis illustrated below.

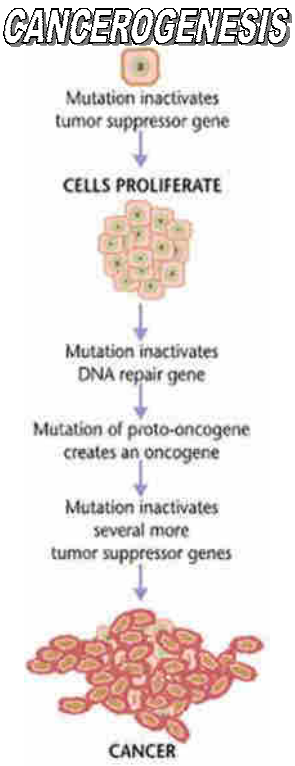

Figure 8. The p53 experiencing negative genetic influences

Figure 9. How oxidative stress and inflammation team up

Things like environmental pollution, radiation, pharmaceutical medications, cell phone radiation, computer & PC screen radiations, Wi-Fi and electro-magnetic frequency pollution etc…all cause oxidation, leading to free-radical damage that leads to chronic inflammation. In addition to these, physical and emotional stress must also be added because they are also oxidative stressors, but are often overlooked.[62] In an example involving brain cancer and brain tumors it can be shown that the ROS species free-radical is one of the most damaging. [63] A scientific study about brain cancers and tumors studied the condition for more that 10 years because of the sharp increase in occurrence in the general population with their cause being ROS oxidative stress.[64] Consequently, the brain is the organ that is the most susceptible to oxidation by free radicals.[65] In this study, experts discovered that brain cancer is linked to extreme oxidative stress leading to free radical damage that causes chronic inflammation. [66] Chronic inflammation as we know is a mediator of many chronic diseases including cancer.[67]

Free radicals and a lack of antioxidants

While free radicals attack cell components, natural and synthetic antioxidants are what should tame and discipline them by donating their own electron and then trapping them to rescue the cellular organelles and DNA from consequent damage, by terminating oxidative chain reactions.[68] Only antioxidants can actually stop free radical damage and only if they are abundant enough and consistently present, so they carry the chief responsibility of inhibiting oxidation and removing potentially damaging oxidizing agents in living organisms.[69] Without antioxidants, disease and aging can quickly and easily occur, when the supplies of antioxidants are low in the body due to oxidative damage the damage is inevitable.[70]

[58] CANCER RESEARCH Mutant p53 Induces the GEF-H1Oncogene, a Guanine Nucleotide Exchange Factor-H1 for RhoA, Resulting in Accelerated Cell Proliferation in Tumor Cells Shinji Mizuarai, Kazunori Yamanaka and Hidehito Kotani DOI: 10.1158/0008-5472.CAN-05-4629Publisher June 2006 www.cancerres.aacrjournals.org/content/66/12/6319

[59] Anoxia and Hypoxia defined www.medicinenet.com/script/main/art.asp?articlekey=2271

[60] Dee Denver assistant professor at OSU, Oxidative Stress is Underlying cause of Huge Numbers Of genetic Mutations Study Finds www.sciencedaily.com/releases/2009/09/090907162318.htm Written by Oregon State University 2009

[61] Dee Denver assistant professor at OSU, Oxidative Stress is Underlying cause of Huge Numbers Of genetic Mutations Study Finds www.sciencedaily.com/releases/2009/09/090907162318.htm Written by Oregon State University 2009

[62] Cancer Lett. 2012 Dec 31 : 327:48-60. Ionizing radiation –induced metabolic oxidative stress and prolonged cell injury

[63] Inflammation, free radical damage, oxidative stress, hydrogen and cancer Oct 2017 dr. sircus.com

[64] Inflammation, free radical damage, oxidative stress, hydrogen and cancer Oct 2017 dr. sircus.com

[65] wiseGEEK: What are the Different Antioxidant Enzymes //m.wisegeek.com/what-are-the-different-antioxidant-enzymes.htm

[66] Inflammation, free radical damage, oxidative stress, hydrogen and cancer Oct 2017 dr. sircus.com

[67] Inflammation, free radical damage, oxidative stress, hydrogen and cancer Oct 2017 dr. sircus.com

[68] What are free radicals? How are they harmful to humans? Nutrition-and-You.com/free-radicals.html

[69] Definition of an antioxidant medical dictionaty. Thefreedictionary/antioxidant

[70] Definition of free radical damage taken from the medical dictionary medical-dictionary.thefree dictionary.com/free+radical

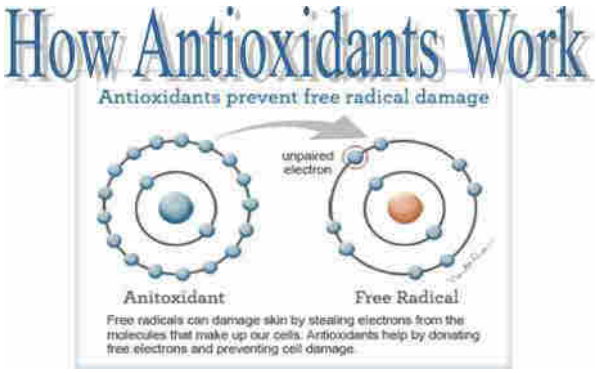

Figure 10. How antioxidants work to prevent free radical damage

Being effective in multiple ways, antioxidants reverse and prohibit oxidants and free radical damage and also do structural repair to cellular components and restoration of cellular function after oxidative stress has occurred.[71] [72] Due to this the body should always have an excess supply of antioxidants available, including thiols and ascorbic acid plus the dietary sources including beta-carotene, lycopene, the mineral selenium and vitamins C and E.[73] Antioxidant enzymes supplies are also necessary as well, like glutathione peroxidase, catalase, superoxide dismutase, glutathione reductase, thioredoxin reductase, heme oxygenase and biliverdin reductase which also help the body. To increase the availability of specific antioxidants under conditions of oxidative stress the cells even have mechanisms that turn on in response to stresses, they can promote levels of intracellular thiols through GSH and thioredoxin.[74] The difference between normal antioxidants and enzymic antioxidants is that while normal antioxidants help repair free radical damage, enzymic antioxidants focus on stopping the damage of oxidation before it occurs. [75] They do this by triggering chemical reactions that rid the body of free radicals and dangerous oxygen in the form of oxides.[76] Anti-oxidants are relevant to the p53 function because they directly assist the body in preventing the free radical damage that leads to genetic instability which negatively impacts the p53 protein.[77]

MDM2 AND THE p53

Aside from oxidative stress prohibiting the p53's actions, Mdm2 is the next most relevant impactful factor because it is the "negative regulator of the p53." Mdm2 stands for "mouse double minute 2 homolog," is a p53 specific E3 ubiquitin-protein ligase. It encodes the p53 in humans and it's the regulator of the p53's tumor suppressing actions.[78]

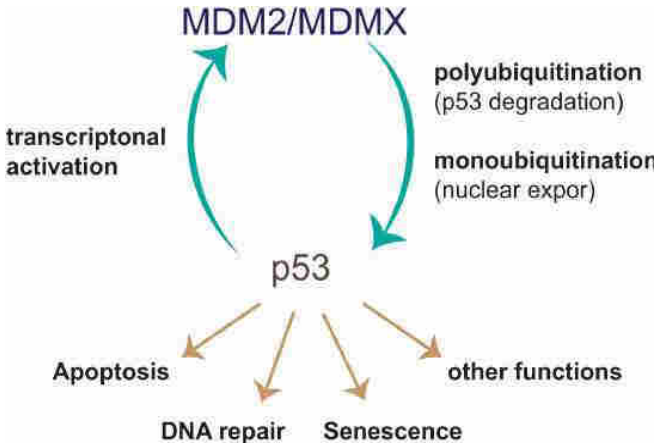

Figure 11. Mdm2 AND THE p53

With the responsibility of controlling the p53's actions and presence, if the p53 becomes too abundant – Mdm2 will downregulate it. Mdm2 is actually produced by the p53 inducible gene, so these 2 molecules are actually linked together through creation and destruction. [79] Through an auto regulating negative feedback loop the p53 and Mdm2 share a relationship and as a team they are responsible for maintaining low cellular levels of p53. In unstressed cells p53 have an unstable, short half-lifespan of 5-30 minutes on the other hand in stressed situations the p53 the p53 is rapidly stabilized by the blocking of its degredation. Mdm2 constantly monoubiquitinates the p53 which is critical in mediating its degradation, this is necessary only when there is no stress or threat to the p53 gene, because without a real threat the presence of excess p53s is not necessary and can cause excessive cell death and apoptosis in normal cells.

In addition to controlling the amount of p53s, Mdm2 also limits the duration and severity of the p53's biological response after a non-lethal stress episode occurs, to prevent the response from lasting too long.[80] Mdm2 can also trigger the p53's degradation and inhibit the p53's transcriptional activation when necessary. Conversely, when the p53 *is* stabilized Mdm2 induces transcription of Mdm2 so that there are increased Mdm2 protein levels available. [81] Studies show that in order for p53s to accumulate during a stress response that the Mdm2 regulatory system has to be interrupted so that it can escape degradation prompted by Mdm2. This shows that Mdm2 needs to improperly function for the p53 this tumor protein to mutate and allow normal cells to mutate and that Mdm2 is main cellular antagonist of the p53 that works limiting its tumor suppressing functions.[82]

The distinct connection here is the p53 – Mdm2 interaction and their negative feedback loop involvement.

The Normal feedback loop is this…
More p53s = Less Mdm2 and Less p53s = More Mdm2

Figure 12 – the MDM2 p53 feedback loop

[71] Definition of free radical damage taken from the medical dictionary medical-dictionary.thefree dictionary.com/free+radical
[72] Antioxidants and Cancer Prevention-National Cancer Institute www.cancer.gov/about-cancer/causes-prevention/risk/diet/antioxidants-fact-sheet
[73] Antioxidants and Cancer Prevention-National Cancer Institute www.cancer.gov/about-cancer/causes-prevention/risk/diet/antioxidants-fact-sheet
[74] Thiol-based antioxidants written by Susan M. Deneke, www.//doi.org/10.1016/S0070-2137(01)80007-8 www.sciencedirect.com/science/article/pii/S00702137010800078
[75] Antioxidants and Cancer Prevention-National Cancer Institute www.cancer.gov/about-cancer/causes-prevention/risk/diet/antioxidants-fact-sheet
[76] Antioxidants and Cancer Prevention-National Cancer Institute www.cancer.gov/about-cancer/causes-prevention/risk/diet/antioxidants-fact-sheet
[77] Antioxidants and Cancer Prevention-National Cancer Institute www.cancer.gov/about-cancer/causes-prevention/risk/diet/antioxidants-fact-sheet
[78] The MDM2 – p53 Interaction written by Ute M. Moll and Oleksi Petrenko Published December 2003 mcr.aacrjournals.org/content/1/14/1001
[79] The MDM2 – p53 Interaction written by Ute M. Moll and Oleksi Petrenko Published December 2003 mcr.aacrjournals.org/content/1/14/1001
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[81] Medical dictionary www.medical-dictionary.thefreedictionary.com/Mdm2
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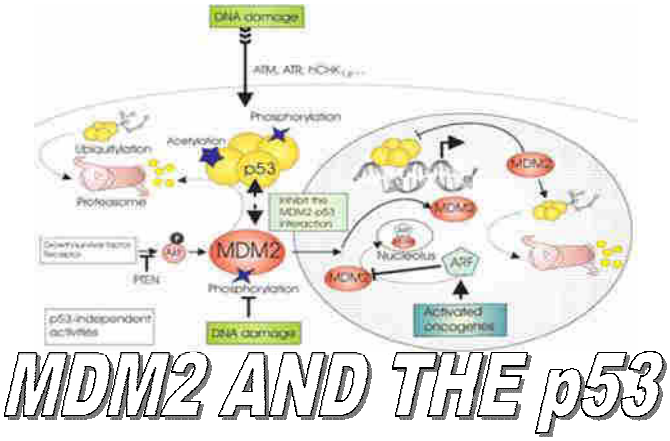

Figure 13 – The p53 and MDM2 in action

So, overall Mdm2 plays a very influential role in controlling the p53 actions through this loop and it also impacts other important cellular settings and is assisted by other factors like Mdmx, HAUSP, ARF, COP1, Pirh2 and ARF-BP1 while on its pathway.[83]

Acid, Hypoxia, Genetic instability and the p53

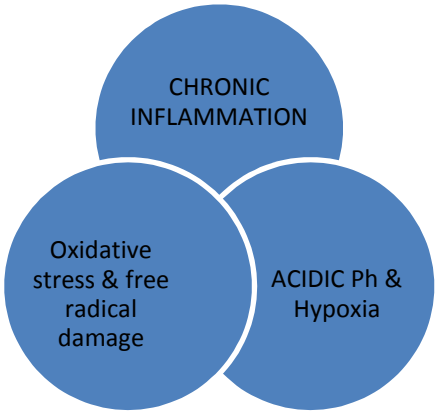

Figure 14. The trilogy of acid, hypoxia and oxidative stress

Having an acidic body ph is very common occurrence and a negative condition that can be caused by oxidative stress. Being acidic is defined as having a body potential hydrogen(pH) level which measures hydrogen ion concentration(H+), if the measure is less than 6 on a logarithmic measurement scale of alkalinity and acid which ranges from 1-14 – this is considered acidic.[84]

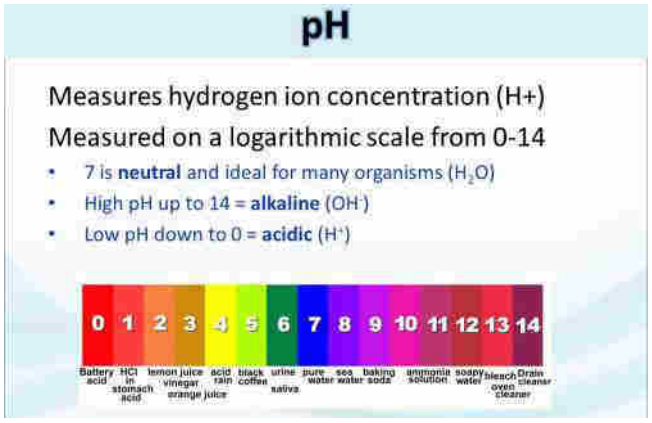

Figure 15. The potential hydrogen chart

Being acidic in pH causes a pathological build-up of toxins, which weaken cellular functions.[85] This type of acidic ph is a very negative and damaging influence on the body that leads to chronic disease because it contributes to low oxygen levels, poor circulation, hypertoxicity and oxidative stress and all of these contribute to genetic instability which can induce the p53 to mutate.[86] Low oxygen levels - a condition called Hypoxia, leads to the poor circulation, which consequently leads cyclically back to having acidic cellular tissue – so the acidic condition becomes cyclical.[87] This cycle of acidity causes a chain of events and which disallow normal oxygen to enter into body tissues which impairs the body's homeostasis and physiological functions. [88] Body tissue with low oxygen levels then requires higher respiration rates. These higher rates then lower body carbon dioxide (co2) levels and cause blood cells to deliver less oxygen to tissues - thus creating more hypoxia – further explaining the negative cycle-loop.[89] While efficient levels of oxygen have a cleansing effect on cells, inefficient oxygen levels allow toxicity to accumulate and increase and greater acidity causing further oxygen deprivation. This leads to greater toxicity accumulation, including cancer causing toxins that debilitate the p53's function as well. [90] With both Hypoxia and an acidic pH causing problems with the circulation of cellular oxygen genetic stability is negatively impacted and the p53's function is directly influenced, leading to problems in it doing its duties of protecting and guarding the genome. [91] Once genomic stability is disturbed, then normal cells easily mutate and disease and pathomechanisms have the advantage; another byproduct of this is the development of the of the tumor microenvironment (TME), the location where mutate cells are housed in the perfect cancer seeding conditions TME. [92]

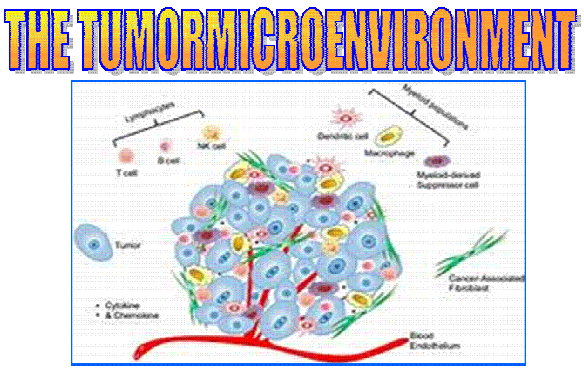

Figure 16. The tumor microenvironment

[83] Medical dictionary www.medical-dictionary.thefreedictionary.com/Mdm2
[84] Acidic definition Merriam-Webster.com

[85] Maintain Acid Alkaline Balance… lookgoodfeelgreatalways.com/acid-alkaline-balance/
[86] Acidity Symptoms: Low body Oxygen cause Low ph in Cells www.normalbreathing.com/s/acidity-symptoms.php
[87] The Tumor Microenvironment: causes and consequences of Hypoxia and Acidity in tumors-Novartis foundation symposium Written by Robert J Gillies Research Update volume 7 Issue 2 p47-49 February 01, 2001
[88] The Tumor Microenvironment: Causes and consequences of Hypoxia and Acidity in tumors-Novartis foundation symposium Written by Robert J Gillies Research Update volume 7 Issue 2 p47-49 February 01, 2001
[89] The Tumor Microenvironment: Causes and consequences of Hypoxia and Acidity in tumors-Novartis foundation symposium Written by Robert J Gillies Research Update volume 7 Issue 2 p47-49 February 01, 2001
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The TME needs hypoxic and acidic conditions to be formed. Once formed it houses mutated cells and keeps them safely protected and incubated until they grow into cancer cells, this friendly environment is perfect for seeding and growing cancer cells into tumors. This TME is the tissue location where cancer cells seed, mutate and tumors set-up and invade.[93] Unfortunately, once the TME is established the p53 has no power to stop the ensuing cancer genesis. [94] Inside the TME because of the acidic ph and hypoxic conditions the genetic stability cannot be recovered, because of the stronghold of these components once the cancer cells and tumor's growth are stabilized, the TME will only strengthen and alter itself by receiving new blood supply through the process of angiogenesis to provide oxygenation in solid tumors.[95] After the cancer genesis gets this assistance and protection in the established TME it will even creates its own new pH levels that are more alkaline, that will support the growth of the cancer cells. The TME is separated form normal cells and completely unaffected by the normal p53.[96]

Mutant p53s become immortal and don't have to die

We know now that normal p53s and cells undergo a variety of biological responses when they are placed in hypoxic, acidic conditions like the TME, and mutate. Subsequent changes including activation of signaling pathways that regulate proliferation and angiogenetic formation of new blood vessels occur; at that point the biggest difference is that the mutant p53 and cancer cells no longer have to die; they can avoid apoptosis and cell cycle suppression. [97] Once mutant they become invincible – both the p53 and the cell are protected by the powerful protective environment of the TME means that they are both nearly unreachable by the body's defense systems.[98] So the TME environment continues protects like a safeguarded stronghold for mutant cancer cells.[99] With the full functioning of the TME, subsequential mutations work along with cancer genesis and start to function only to assist tumor growth - protecting the cancer, its' cells and mutated genes alike including the mutated p53.[100] [101] It is in this mutated state that genes and cells adapt to specific hypoxia-response pathways allowing tumors to survive and grow even within the low oxygen conditions, which is especially with poor prognosis for cancer sufferers because they develop a resistance to treatment including radiation therapy. [102] Hypoxia also includes another important factor which is the hypoxia inducible factor 1alpha which is a positive factor found in all solid tumor growth."[103] The transcription factor hypoxia-inducible factor HIF) -1alpha is an important mediator of the hypoxic-response of tumor cells and it controls the up-regulation of a number of factors important for solid tumor expansion, including the angiogenic factor vascular endothelial growth factor (VEGF)."[104] What this shows is that cancer cells have a systematic mechanism ready to respond to hypoxic conditions. The TME starts to makes its own fuel. [105] [106] This is the beginning of the end because once the TME begins to do this and initiates the use of glucose based energy to provide fuel for cancer cell growth the cellular environment has now switched over from being oxygen fueled to being glycolic fueled – and at that point the p53 has already mutated and been deterred from its proper path and course of action so it can no longer provide assistance to prevent normal cells from mutating or protect the body. [107] [108] [109] All of these major oxidative influences are directly linked to the Warburg effect. [110]

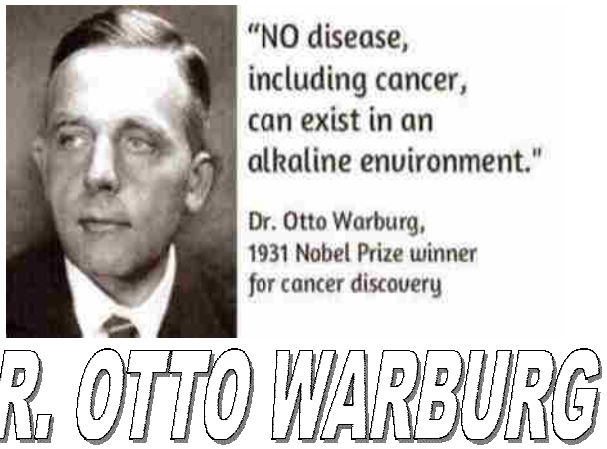

Figure 17. Dr. Otto warburg

[93] The Acidosis/Hypoxia Cancer Link www.dragonfly75.com/eng/hypervent.html
[94] The Tumor Microenvironment: causes and consequences of Hypoxia and Acidity in tumors-Novartis foundation symposium Written by Robert J Gillies Research Update volume 7 Issue 2 p47-49 February 01, 2001
[95] The Tumor Microenvironment: The Making of a Paradigm Written by Issac P Witz Cancer Microenvironment 2009 2 (suppl 1) : S9-S17 DOI 10.1007/s12307-009-0025-8
[96] The Tumor Microenvironment: The Making of a Paradigm Written by Issac P Witz Cancer Microenvironment 2009 2 (suppl 1) : S9-S17 DOI 10.1007/s12307-009-0025-8
[97] The Acidosis/Hypoxia Cancer Link www.dragonfly75.com/eng/hypervent.html
[98] The Tumor Microenvironment: The Making of a Paradigm Written by Issac P Witz Cancer Microenvironment 2009 2 (suppl 1) : S9-S17 DOI 10.1007/s12307-009-0025-8
[99] Ziwei Dai and Jason W. Locasale Metabolic pattern formation in the tumor microenvironment department of pharmacology and Cancer Biology, Duke University, Durham, NC, USA molecular systems biology webpage www.m.msb.embopress.org/content/13/2/915
[100] Oxidative stress and P53 mutations in carcinogenesis of iron overload associated hepatocellular carcinoma Written by Marroqi AJ, Khan MA, Van Gissel HE, J Natl Cancer Inst, 2001 Nov 7; 93(21): 1652-5 PMID: 11698570 - discusses Epigenetic mutations in P53 - ncbi.nlm.nih.gov/pubmed/11698570
[101] The Acidosis/Hypoxia Cancer Link www.dragonfly75.com/eng/hypervent.html
[102] Hypoxia – a key regulatory factor in tumor growth written by Harris AL Nat rev cancer, 2002 Jan;2(1):38-47 www.ncbi.nih.gov/pubmed/11902584
[103] Hypoxia-inducible factor1alpha is a positive factor in solid tumor growth Cancer Res,2000Aug 1;60(15):4010-5 Written by Ryan HE, Poloni M, McNulty W, Wlson D… www.ncbi.nlm.nih.gov/pubmed/10945599?ordinalpos=1&itool=PPMCLayout.PPMCAppController.PPMCArticlePage.PPMCPubmedRA&linkpos=2
[104] Hypoxia-inducible factor1alpha is a positive factor in solid tumor growth Cancer Res,2000Aug 1;60(15):4010-5 Written by Ryan HE, Poloni M, McNulty W, Wlson D… www.ncbi.nlm.nih.gov/pubmed/10945599?ordinalpos=1&itool=PPMCLayout.PPMCAppController.PPMCArticlePage.PPMCPubmedRA&linkpos=2
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[107] The Acidosis/Hypoxia Cancer Link www.dragonfly75.com/eng/hypervent.html
[108] Oxidative stress and P53 mutations in carcinogenesis of iron overload associated hepatocellular carcinoma Written by Marroqi AJ, Khan MA, Van Gissel HE, J Natl Cancer Inst, 2001 Nov 7; 93(21): 1652-5 PMID: 11698570 - discusses Epigenetic mutations in P53 - ncbi.nlm.nih.gov/pubmed/11698570
[109] Ziwei Dai and Jason W. Locasale Metabolic pattern formation in the tumor microenvironment department of pharmacology and Cancer Biology, Duke University, Durham, NC, USA molecular systems biology webpage www.m.msb.embopress.org/content/13/2/915
[110] p53 mutations in Cancer WRITTEN BY Muller PA, vousden KH, Nat cell boil. 2013 Jan;15(1): 2-8 www.ncbi.nlm.nih.gov/pubmed/23263379

Warburg explains how mutant p53s are linked to acid ph and independent glycolic based energy production

Dr. Warburg studied cancer for many years and looked closely at the cancer causing mechanisms.[111] His "Warburg theory" also known as the "Warburg Effect" specifically explains how tumorigenesis is driven by insufficient respiration that damages the mitochondria and how as a result of this cancer cells choose to ferment to create their own fuel by glycolic fermentation followed by lactic acid fermentation in the cytosol - instead of respire.[112] This independence gives cancer cells a great advantage because with it they become self-sufficient because this gives them more control and power over their own fate and proliferation.[113] The Warburg theory describes the two very different pathways of the p53 can allow a cell can take. There is the oxygen *dependant* pathway of oxidative phosphorylation and the oxygen *independent* pathway of glycolysis which is less efficient in generating ATP but can still generate ATP power for the cell; Warburg discovered that the p53 allows the cancer cell to choose the oxygen independent pathway of glycolysis. For this discovery he won the 1931 Nobel Prize. Recently it was discovered that the p53 is directly involved in mediating metabolic changes in cells that are under physiological and pathological conditions of stress. It regulates energy metabolism and oxidative and amino acid metabolism through the process of balancing glycolysis and oxidative phosphorylation (OXPHOS) and by autophagy pathways. [114] The p53 is actually activated by metabolic stress through AMP-activated protein kinase (AMPK) and by mTOR signaling pathways. [115] The p53 also indirectly influences energy metabolism through regulating glucose transporter expressions, glutaminase (GLS2) and fatty acid synthase (FAS). The p53 also regulates autophagy to provide cell metabolites for surviving through damage regulated autophagy modulator (DRAM1).[116]

Figure 18. Zinc and Copper

Minerals, metals and the p53

Another important influencer of the p53's function is the presence or lack of certain minerals and metals within the body.[117] Minerals and metals are relevant because they are vitally essential for the proper functioning of enzymes and proteins, the brain and organs, bone and teeth formation, immune system function, oxygenation of the blood and the body, control of physicochemical processes and overall physiological function and homeostasis.[118] When metal or minerals are in excess or deficiency, free radicals form, which causes genetic instability and damage to the DNA protection from diseases like cancer.[119] The p53 is directly influenced by these metals because they cause the p53 to unfold and lose its ability to function, the p53 needs to fold up and bind with zinc in order to function properly.[120] Zinc is especially vital in the fight against cancer because it is the key metal that plays a very most important role in the function of the p53 and the immunity.[121] This is because Zinc is an antioxidant that the p53 needs to balance from ROS damage to do its work, without Zinc the p53 cannot balance properly. [122] Zinc supports more than 300 enzymatic actions needed for proper physiological function, it supports physical growth and development, regulates all hormones, decreases inflammation in the body, reduces cancer cell development and supports the immune system overall which is why it is needed for fighting cancer.[123]

Superoxide dismutase enzymes (SODs) the intercellular antioxidants needed to fight off oxidation are also reliant on Zinc for proper function and structure, and to inhibit infections and toxic debris accumulation.[124] These SOD enzyme antioxidants also protect the cell's genomic sequences responsible for gene expression including the p53, so this is also a key connection to the p53's behavior. [125] Therefore, Zinc deficiency, excess or toxicity can severely impair the p53's function.[126] Also, within the cancer TME, excessively high sugar levels from lactose based metabolism prevent Zinc from being absorbed and utilized properly by the body and this leads to low zinc levels throughout, which leads to poor wound-healing and a disempowered immune system.[127] [128]

[111] WARBURG https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/warburg-effect
[112] Alfarouk KO, Verduzco D, Rauch C, Meddathir AK, et all, 2014 Glycolysis,, tumor metabolism, cancer growth and dissemination, A new pH-Based etiopathogenic perspective and therapeutic approach to an old cancer question. Oncoscience. 1(12): 777-802 doi:10.18632/oncoscinece.109 PMC 4303887
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[122] Toxicology Research Issue 3, 2015s, Metal toxicity and the p53 protein; and intimate relationship written by Vinaya M.Phatak and Patricia A.J. Muller www.pubs.rsc.org/en/content/articlelanding/2015/tx/c4tx00117f#!divAbstract
[123] The truth about cancerthetruthaboutcancer.com/zinc-deficiency-cancer/
[124] Toxicology Research Issue 3, 2015s, Metal toxicity and the p53 protein; and intimate relationship written by Vinaya M.Phatak and Patricia A.J. Muller www.pubs.rsc.org/en/content/articlelanding/2015/tx/c4tx00117f#!divAbstract
[125] Toxicology Research Issue 3, 2015s, Metal toxicity and the p53 protein; and intimate relationship written by Vinaya M.Phatak and Patricia A.J. Muller www.pubs.rsc.org/en/content/articlelanding/2015/tx/c4tx00117f#!divAbstract
[126] Vinaya M. Phatak and Patricia A. J. Muller Metal toxicity and the p53 protein: an intimate relationship toxicology Research Journ. Issue 3, 2015 www.pubs.rsc.org/en/content/articlelanding/2015/tx/c4tx00117f#!divAbstract
[127] TRACE ELEMENTS AND GLUCOSE DISORDERS n Written by David Watts PhD. Director of Research, TRACE ELEMENT INC. Newsletter volume 11, 1999 June Number 2
[128] MERCK MANUAL Metabolic Acidosis www.merckmanuals.com/professional/endocrine-and-metabolic-disorders/

Copper

Copper is also highly crucial and a very important metal needed by the body, it is the mineral partner of Zinc, so together as a pair they need to stay balanced. An inappropriate level of Copper displaces Zinc levels leaving the ratio imbalanced, which again leads to p53 problems. Low levels of Zinc or excess levels of Copper or other heavy metals like lead, aluminum, cadmium and mercury all damage the p53 protein preventing it from being able to do its job of policing and regulating the cell cycle.[129]

Discussion - using real facts to demystify the p53 mystery

With several factors discussed already, the mystery of how and when the p53 switches and mutates is beginning to dissolve, as the truth is revealed. The information elucidated so far clarifies how easily the p53 can be influenced to veer off-path, prompting mutation to easily occur. The overall combination of epigenetic factors, oxidative stress, Mdm2 deregulation, and metal and mineral imbalances leading to p53 mutation and cancerogenesis is crystal clear.

The conglomerative cascade of events leading to the p53 mutation progresses through a series of steps as follows

- Epigenetic factors cause oxidative stress,
- Oxidative stress causes free radical damage
- Free radical damage causes genetic instability
- Genetic instability deregulates MDM2 function
- These steps lead to the mutation of the p53 and normal cells
- Once mutation occurs the p53 easily translocation into the cell nucleus
- Meanwhile, acidosis leads to hypoxia and more acidosis - causing more oxidative damage
- acidosis and hypoxia provoke the body to set-up Tumor Microenvironments
- cancer cells seed inside the Tumor Microenvironments
- The tumor microenvironments produce more lactic acid leading to more acidosis and hypoxia and cancer seeding
- The Warburg effect occurs, supporting protumorigenic cellular activities, resulting in oncogenesis
- P53 can no longer impact the seeded cancer cells

This is all clearly illustrated in the figure below.

Acknowledging the truth and going beyond the mystery

Coming to terms with the p53 mystery means first acknowledging just how many negative things truthfully influence it that are caused by our own environment and lifestyle, in the form of epigenetic factors. This is a difficult truth to face because as humans it means that aside from the scientific level of what mysterious microscopic phenomena are occurring in the 17th chromosome incapacitating the p53's function that *we* also have to take a bigger overview of what is happening on the larger scale as well. Taking responsibility for guarding and protecting the health of the human race is a sobering task, and something the p53 can barely keep up with.

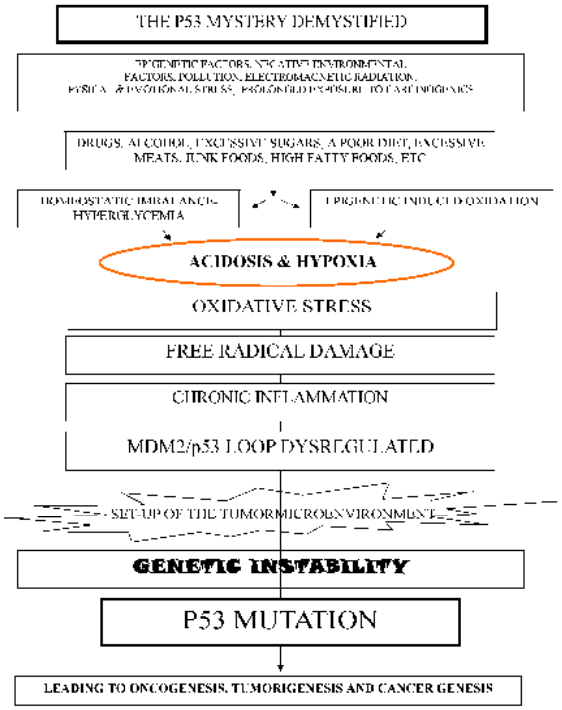


Figure 18. The p53 flowchart to its demise

Look at how we live our lives - this modern age is filled with lies. Like exposure to chemical toxins, excess pollution, electro-magnetic radiation, stressful work experiences, fast-paced lifestyles, drugs, drinking, cigarette smoking, limited sleep, all combined with diets filled with excessive sugars, processed and chemical laden foods, junk foods, and excessive grilled meat consumptions, all of this leading us to poor health. Also, the fact that people exercise the body less than they ever have with the modern lifestyle – which is filled with conveniences - allowing us to take the mechanized, easy route to getting things done, we have to look at what we are actually doing to contribute to our own health problems by weakening the body. In fact, when cancer was first being discovered in the past centuries, lifestyle causative factors weren't as relevant as they are today, environmental pollution was less, processed foods were still rare and hard work was still the way of the world – though inconvenient compared to our modern lifestyles of today, these things actually kept us healthier in that past.[130] Unfortunately, this is where many of the truths of the mystery of the p53 are hidden – shrouded in what we consider the modern "norm." This is a hard truth to face but fortunately, with strong prevention and higher expectations of behavior modification from patients, we can use powerful preventative maneuvers and develop ways that will help the p53 stay on tract so it can continue guarding the genome and helping us avoid cancer before it gets started. [131] [132]. The fact that our healthy cells are so easily influenced by our own negative self-induced behaviors, lifestyle and environment causing epigenetic stressors, is karmic but it makes understanding the p53's switch less of mystery and more of a

[129] Toxicology Research Issue 3, 2015s, Metal toxicity and the p53 protein; and intimate relationship written by Vinaya M.Phatak and Patricia A.J. Muller www.pubs.rsc.org/en/content/articlelanding/2015/tx/c4tx00117f#!divAbstract

[130] Real Cause of Cancer- detoxifynow.com/real_cause_of_cancer.html

[131] Visconti R, Grieco D. New insights on oxidative stress in cancer. Curr Opin Drug Discovery Development. 2009;12:240-245 Pubmed www.ncbi.nlm.nih.gov/pubmed/19333869

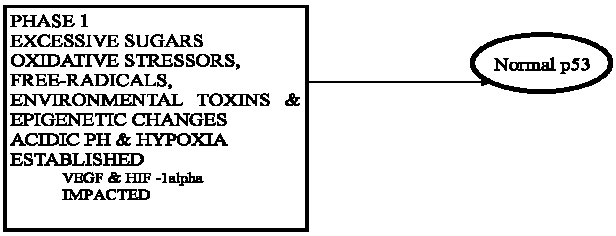
[132] Oxidative stress and P53 mutations in carcinogenesis of iron overload associated hepatocellular carcinoma Written by Marroqi AJ, Khan MA, Van Gissel HE, J Natl Cancer Inst, 2001 Nov 7; 93(21): 1652-5 PMID: 11698570 - discusses Epigenetic mutations in P53 - ncbi.nlm.nih.gov/pubmed/11698570

case for self-examination of ourselves and our environment. Acknowledging that modifying our own behavior is needed to bring the balance back to our health takes a lot of the focus away from the p53 failing and sends it circling back onto us – meaning we need to find ways to change how we our living to prevent the p53's mutation from ever occurring. Additionally, knowing that cancer cells exist and thrive separately from the body once they seed and become housed in the Tumor Microenvironment, with the p53 having no way to impact them, means that prevention is key to stopping cancer - to stop it before it setups - not after.[133] [134] This mean with stronger prevention we can give more power back to the p53.

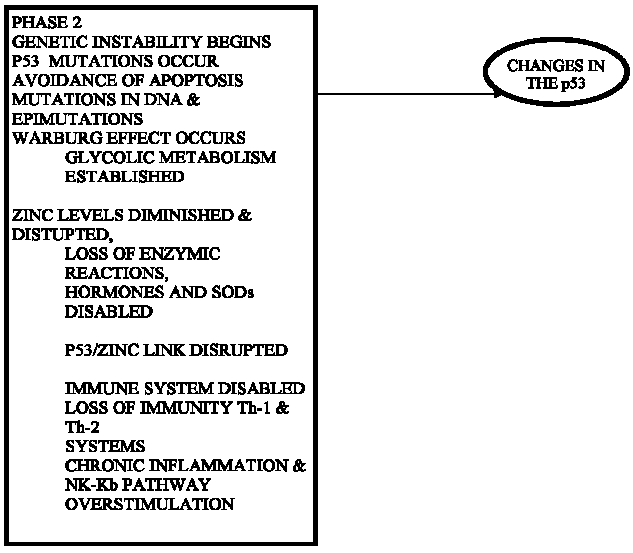
Overall the p53 switches in 3 phases illustrated below

Tables the 3 phase breakdown

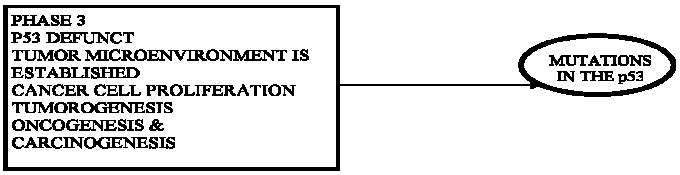
Conclusively the 3 phase breakdown is listed below. Here are the 3 phases.



Phase 1 explained: This is phase 1, it begins when there is no longer normal homeostasis within the p53 and it no longer works properly by policing cells and guarding them. This is when abnormal and imbalanced body conditions overwhelmed by excess oxidative stress caused by epigenetic factors including life stress, an acidic ph, hypoxia start to overwhelm the cell, leading to genetic instability- during this phase the p53 gene should guard and protect – and in these moments the p53 is still normal but being negatively influenced, and going towards change. This is also a phase that is reversible, if drastic lifestyle changes are made.



Phase 2- It is during Phase 2 that many critical events occur, starting with the atmosphere of genetic instability and the mutation of the p53 is inevitable, and because the p53 mutates it now supports mutations within the cells as well and allows them avoid apoptosis. It is during this phase that the immune system is disabled, because zinc levels are deficient so the immune system is directly impaired as well as all enzymic reactions, hormonal balances also occur, and chronic inflammation occurs due to the disruption of the NK-Kb pathways being over stimulated they cannot perform their duties properly. This is the phase where cells now use fermented sugars to supply fuel for ATP needs as opposed to oxygen. During this phase while the immune system is debilitated massive cellular and genetic changes occur and the p53 no longer protects against cancer being established.



Phase 3 – this is the final phase where the p53 is actually dysfunctional and cancer is being formed in the TME, normal cells have totally transformed, this phase is characterized by changes at the cellular, genetic and epigenetic levels accompanied by abnormal cell division – dysplasia and hyperplasia. The tumor microenvironment is fully established and housing these new cancer cells and a reciprocating relationship is developed between them to ensure survival of the cancer. Cancer's development and metastasis all easily occur during this phase without any p53 protection or security.

Conclusion

In conclusion, the "mystery of the p53" is actually not a mystery at all but more so a "story of our modern existence and how it negatively impacts our health." The p53's downfall and demise is easily explained by epigenetic factors leading to a 3 phase cascade of conditions that provoke its changes and mutation. These phases include events mainly provoked by epigenetic factors that result in oxidative stress that leads to genetic instability and the p53's malfunction and mutation thus allowing cancer cells to easily develop unchecked. After analysis, demystifying the p53 means acknowledging the epigenetics influences within our lives. The act of preventing p53 mutation is not just medical, but also ethical because it places a major part of the responsibility directly into our own hands. It is apparent that guarding its integrity is key in preventing cancer but doing it before and not after is the crucial aspect of this equation. Knowing the p53 can be so easily provoked by epigenetic factors means avoiding negative lifestyles and causative factors. Supporting a negative lifestyle means supporting genetic instability that "the guardian genome" cannot overcome and it will continue to suffer and eventually mutate and even support mutations of normal cells and cancer genesis indefinitely. So, we have to make the choice. We change this. With proper maintenance of the body, support from anti-oxidants, as well as keeping the body constitution balanced, and limiting exposure to environmental stressors we could actually lower oxidative stress thus preventing rogue mutations from occurring within cells and in the p53 and also preventing the establishment of the TME. It is then that the p53 will also be supported in doing its job properly. With proper support, the p53 will thrive as the "guardian of the genome."

[133] The Acidosis/Hypoxia Cancer Link www.dragonfly75.com/eng/hypervent.html

[134] Oxidative stress and P53 mutations in carcinogenesis of iron overload associated hepatocellular carcinoma Written by Marroqi AJ, Khan MA, Van Gissel HE, J Natl Cancer Inst, 2001 Nov 7; 93(21): 1652-5 PMID: 11698570 - discusses Epigenetic mutations in P53 - ncbi.nlm.nih.gov/pubmed/11698570

A way to fix this p53 problem

The way to fix this problem is to begin with the lifestyle changes in the way we live, the places we live, the things we eat and the things we do. Changes like these, appear simple, but are difficult for some – either way they are a major part of preventing cancer and create a dividing line which separates those "who get cancer" from those "who don't."

In retrospect, from a microscopic perspective the p53's behavior seems mysterious, but looking from a macroscopic grander scale the situation is easily put into perspective and what is revealed is that without the continual interference of being overwhelmed by chronic genetic instability the p53 will thrive. Once this has been fully addressed, we can move forward with new treatment methods.

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