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Commentary

Precision Medicine for Childhood Cancers: Role of Epigenetics in Childhood Cancers

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Abstract

The prospect of having a child diagnosed with a cancer is a heart-wrenching experience and one in which subjects the child to painful and long- term consequences. Given the recent explosion of scientific understanding of human carcinogenesis, which involves both genetic and environmental factors playing a role in the development of those cancers, new concepts of "Precision Medicine", "Personalized Medicine" and "Environmental Medicine" have been generated to mobilized new technologies for the prevention and treatment of childhood cancers. Much of this new thrust has been based on technologies related to "genomics", or to the major genetic biomarkers that presumably could predict the major "drivers" in the cancer. Without a doubt that there are various genes that can predispose an individual to a given cancer, the roles that "epigenomics" and genetic factors has been widely ignored. This "Commentary" will explore how the multi-step, multi-mechanism process of human carcinogenesis involves the interaction of both the genetic and epigenetic factors during the in utero-perinatal developmental period. Specifically, it will be assumed that the "epigenetic" component of carcinogenesis is the real "driver" of childhood cancers and a specific cellular mechanism will be offered for the Barker hypothesis that happens during in utero development that leads to cancers later in life.

Keywords: *Precision Medicine; Personalized Medicine; Environmental Medicine; Epigenetic Toxicology; Childhood Cancers; Gap Junctional Intercellular Communication; Cancer Stem Cells*

"Personalized medicine is the latest promise of a gene-centered biomedicine to provide treatments custom-tailored to the specific needs of patients. Although surrounded by much hype, personalized medicine at present lacks the empirical and theoretical foundations necessary to render it a realistic long-term perspective. In particular, the role of genetic data and the relationship between causal understanding, prediction, prevention, and treatment of a disease need clarifying"

Alex Gamma [1].

Introduction

What Is (Are) The Driver(s) Of Normal And Abnormal Childhood Development?

Given the unique human conceptus has no choice in the genes it receives, nor does the human embryo, fetus or even the neonate have a choice in the quality of the in utero or neonatal environments, there must be a critical focus on trying to control those factors that might influence the expression of the conceptus's genes. One might even argue that the young human being has little choice in the social and cultural environments, due to economic, religious, and political environments that he/she finds itself. With the global health issues of today being the result of the collision that is occurring between our slow biological evolution of genes needed to survive, fundamental issues of nutrition for individual and species survival are needed to meet the rapid cultural evolution that is impacting every dimension of our survival [2-4]. The requirements for clean air, water, uncontaminated foods, unpolluted environments, adequate calories and nutrients for specific human activity at each stage of development, adequate psychological and social environments for the development of self-worth depends on a solid understanding of the science of human biology and human development.

Since we are unique human beings, by virtue of the unique genes we inherit (acting as a "blue print"), that interacts with historically unique physical, chemical, biological, social and cultural environments (acting as carpenters, plumbers, electricians and stone masons, working on the blue prints- our DNA), the end result is a unique "us" (even identical twins, with the same DNA or blue print, end up as unique persons, not identical beings). Renee Dubos said it best when he stated:

"We resemble our progenitors because we derive from them our genetic endowment; but our genes do not determine traits by which we know a person. They only govern the responses that the person takes to the environmental [dietary] stimuli. Individuality progressively emerges from those responses".

R. Dubos [5]

Today, with exploding sophisticated technological approaches to study human biology (next generation sequencing; stem cell biology; human genomic studies; epigenomic studies), there is an emerging prospect (or hype) that, by using these techniques and new scientific knowledge of human development with the concepts of "precision medicine" [6], "personalized medicine" [7] and "environmental medicine" [8], one might be able to be better at diagnosing, prognosticating, preventing and treating diseases in the individual person. However, much of the hope, based on these new concepts, is that DNA is the prime "driver" for good health or predicted disease. Of course, while inherited mutations (gene and chromosomal) do play a role in both germline and somatic diseases, a challenge is made that the prime drivers of human diseases are not mutations, but epigenetic changes.

How do Mutations and Gene Expression Alterations Contribute to Human Diseases, Particularly Childhood Diseases?

While this "Commentary" is not intended to reiterate the known science of various kinds of gene and chromosomal mutations, such as point mutation, deletion mutation, gene duplication, chromosomal deletions, aneuploidy, polyploidy, translocations, etc., the molecular mechanisms of each are different. The point to be made here is, that by using point mutagenesis as an example, we can and should try to minimize point mutagenesis. However, we will never reduce the risk for mutation production in the human body to zero levels. In this Commentary, childhood cancer will be used as one example to illustrate how the different mechanisms of toxicity (mutagenesis; cytotoxicity and alterations of gene expression) can influence the pathogenesis of cancer (and other diseases). Also, while the issue of childhood cancers includes both prevention and treatment strategies, the aim here will focus on prevention, since the current treatment strategies, which are in a state of a major paradigm shift (i.e., to target "cancer stem cells" [9]) are beyond the scope of this Commentary.

The rationale for this examination of the factors and mechanisms, that could influence childhood cancers and other diseases, is for the purpose of trying to reduce the risks to these diseases. This will be provided by a few human genetic syndromes. Xeroderma pigmentosum individuals are born with two recessive genes that code for proteins that cannot repair lesions in skin cells that have been exposed to ultraviolet light from the sun [10,11]. Consequently, those cells that survive these unrepaired UV light DNA lesions have many mutations [12-14]. These mutations might be classified as "errors of DNA repair". However, to illustrate the fact that, even with these mutated DNA repair genes in all the cells of the XP body, usually only those skin cells will manifest cancers years later [15].

To understand the role of these mutations in skin carcinogenesis (or any other kind of cancer), one must understand that all cancers start from a single normal cell. Once a critical mutation has occurred in a few of the 25,000 genes of our genome, that mutation allows normal cells to become "immortalized" or be prevented from terminal differentiation. That cell is classified as an "initiated" cell. It is, however, not a cancerous, invasive or a metastatic cancer [16,17]. That initiation process is an irreversible one and it is believed to be due a mutational event, such as demonstrated in human skin cancer cells [14].

Another genetic human syndrome, the Blooms syndrome, can form mutations throughout the whole body [18]. These individuals have normal DNA repair but they seem to have an inherited defect in a gene that allows mutations to be formed anytime when the stem cell replicates. In other words, they could be classified has forming mutations via "errors of DNA replication" [19]. This has relevance to situations, such as persons not ever being smokers or even exposed to down-stream smoke [20,21]. In other words, every time an organ-

specific adult stem cell divides, there is a finite chance of an "error in DNA replication" mutation has been produced. We all has these spontaneous or "errors of DNA replication" in all of our organs.

Last, another human genetic syndrome, the Down syndrome, is a very unique syndrome that not only leads to birth defects, leukemia, predisposition to diabetes, cardiovascular diseases, premature aging, and, in those that live long enough, a high risk for Alzheimer's disease and possibly to autism-like diseases [22-24]. To classify these individuals, while they have a chromosomal mutation leading to trisomy 21, the underlying problem is not point mutations in any of the three copies of genes on chromosome 21, but it is due to altered gene regulation of those genes. In other words, this syndrome, brought about by the inheritance of three 21 chromosomes, causes abnormal epigenetic expression of those normal genes that can lead to a wide variety of chronic diseases. A chromosomal mutation that causes epigenetic disruption of normal genes.

All of us, who are not XP individuals, are exposed to sunlight every day, and, while skin cancers are the most prevalent cancers, many of us will go through our life without getting a skin cancer. Yet all of us have "initiated" skin cells. To go from that single initiate cell to a full- blown invasive and metastatic cancer in adults, it takes decades. Therefore, there is another process, i.e., the "promotion" process, that can expand the single initiated cell non-mutagenic means, i.e., epigenetic mechanisms, that can stimulate the selective expansion of the initiated cell and the prevention of the self-suicide of that cell by apoptosis [25,26]. This process works to block the mitogenic suppressive effect that normal cells have on the single initiated cell. The process of promotion can be brought about by endogenous factors (growth factor, hormones, cytokines) and exogenous factors (pollutants, drugs, dietary components, irritants, cytotoxicants, behavioral choices- smoking, alcohol, lack of exercise, etc.), that all have threshold levels of action and all must be acting on the initiated cells in the absence of anti-promoters [27,28]. In other words, the promotion phase is potential interruptible or possibly reversible in the adult [29]. The mechanism of tumor promotion, while not universally accepted, seems to involve that blockage of cell-cell communication by secreted soluble negative growth regulators or by gap junctional intercellular communication [30].

The sustained and long- term exposure to these non-mutagenic agents can stimulate the initiated cells to expand and not die by apoptosis, thereby, allowing the initiated clone to become a benign lesion, such as papilloma in the skin, a polyp in the colon, enzyme-altered foci in the liver and a nodule in the breast. However, during this promotion or clonal expansion of the initiated cell, each time the cell replicated it can introduce more point/or chromosomal mutations, changing its genotype and phenotype to become invasive and metastatic. From the standpoint of cancer prevention, the promotion phase, which requires a sustained exposure to epigenetic agents at threshold levels, should be viewed as the most efficacious approach to prevention [31].

Now to direct this information to childhood cancers, this initiation/promotion/progression process, that seems to explain adult cancers, might seem irrelevant to childhood cancers. However, in spite of the patterns of childhood cancer being different to adult cancers in any culture [32], and because the treatment of cancers seemingly more effective in children than in adults [33], there might be a way to rationalized this Initiation/promotion/progression model to childhood cancers.

While this Commentary has not tackled the question of what is the "target" cell for the initiation event, it will be assumed, for the sake of brevity, that the adult organ specific adult stem cell, which exists in all organs,[that is how a single organ-specific stem cell can make tissues of that organ, such as skin, brain, liver, kidney, pancreas, gut, etc.], is the target cell [34-37]. In other words, the stem cell hypothesis [38-44], rather than the "De-differentiation "or Re-programming "hypothesis" [45], can explain the initiation/promotion/progression process of human carcinogenesis. Several examples of the stem cell hypothesis have been experimentally demonstrated [42,46]. Once an organ-specific adult stem cell has a critical gene mutated, either by an "error of DNA repair" or an "error of DNA replication", it remains in an un-terminally differentiated state, which can either remain that way throughout life or be expanded by the epigenetic process of promotion to accrue addition genetic/epigenetic changes need to become invasive and metastatic.

After conception, that single zygote can now be stimulated to proliferate, differentiate and even apoptose in a very delicate, orchestrated homeostatic process, such that at each developmental stage, these cellular events must occur at the right time. That homeostatic process involves specific signals, by extra-cellular secreted and direct extracellular adhesion or extracellular contact which triggers intra-cellular signaling and gene expression. At the same time, these intracellular signals also can modulate gap junctional inter-cellular communication between contiguous cells. If that well- orchestrated process is disrupted, development can be dramatically altered [47]. There is no going back, because development must go on in the concatenated manner. Embryo lethality, birth defects and other post-birth disease effects, such as the thalidomide-induced limb deformities [48] or DES-induced vaginal cancers [49], which can occur, i.e., via the Barker hypothesis [50].

Back to childhood cancers. Even in the cases of non-hereditary cancer in children, it would seem that it would be difficult for the initiation/promotion/progression phases to provide an explanation for early appearances of the cancers seen in children. First, because there is rapid stem cell proliferation to go from one organ-specific stem cell to form organs in a few years after birth when growth is still happening, "errors of DNA replication" must be happening. That is, children are producing more mutations in stem cells than in adults. Second, promotion of these initiated stem cells is by all the hormones and growth factors that are needed for neonatal and adolescent growth. In addition, the nutrients and dietary factors can be agents, i.e., promoters, that can cause the clonal amplification of these initiated cells.

Now another speculation that might explain either a resistance or susceptibility to cancer later in life involves an interaction of epigenetic agents with organ-specific adult stem cells during in utero development. If one assumes that the adult organ-specific adult stem cell is the target cell for the initiation event, then it might be reasonable to assume that any increase or decrease in any organ-specific stem cell might increase or decrease the risk to the initiation event because the "target-size" for the initiating event would occur [2,51,52]. One might interpret the frequency of human breast cancers in the Japanese women during the Second World War as evidence that the Japanese diet at that period helped to reduce the frequency of breast cancers of both the control, non-atomic bomb exposed population and the exposed population [53,54]. Given the extremely low frequency of breast cancers in the non-exposed population allowed any small increment of breast cancers to be shown, statistically, in the exposed population [55]. In an experiment system, human adult breast stem cells have been shown to be target cells for neoplasic transformation *in vitro* [51, 56]. In addition, when these normal human breast adult stem cells were exposed to genistein, an antioxidant found in soy products, the cells differentiated [57].

Since the Japanese women at that period of time ate the traditional Japanese diet, which consisted of low caloric amounts, vegetables, raw fish, rice, tofu and green tea and a lack of cigarette smoking, plus much physical exertion, it is speculated that any female fetus exposed to its mother eating this diet, the genistein might cause premature differentiation of the breast anlage, such that after birth and during puberty, her hormones would have few breast stem cells to make breast tissue, let alone enough breast stem cells to be targets for breast stem cell initiation [58]. If this is correct, this could be a cellular mechanistic explanation of the Barker hypothesis. In this case, the in utero decrease in organ-specific stem cells would reduce the risk for breast cancer later in life. Of course, one could easily assume, other factors, in utero, would increase an organ-specific adult stem cell in another organ, such as the blood tissue, to increase the risk after birth, leading to leukemia that was seen in those young individuals exposed to the atomic bombs.

Global Health, One Health and Human Political Ethics

The concept of "One Health" usually is defined as the interconnectedness of environmental health with animal health and human health [59]. Global health is the empirical demonstration, at any given time, of the patterns and frequencies of any human disease, childhood or adult, and acute and chronic diseases [60]. What is normally ignored in trying to determine the link between a One Health understanding of the physical, chemical and biological components of the total environment with both animal and human health is the concept of evolution [61]. Even if there were no humans on earth, both the physical environment, the microbial/plant and animal worlds would be changing. With human beings in the current mix of living organisms, "culture" is laid on top of physical and biological evolution. Therefore, today, human cultural evolution is colliding with the millions of years it took to have biological evolution evolve and select those genes need to

extract energy from food for individual survival and specie s survival [2-4]. Just to focus on human survival, our ancestors, originally emanating from Africa but later having its diaspora to all regions of the earth, had ethnic groups that survived on various distinct local foods. That means, to find a "One Health" strategy, for instance, for the creation of the most healthy, cancer free diet, will be an impossible task.

When one sees the patterns of both childhood and adult cancers differing in the different regions of the Earth (tropical, temperate, artic, arid, etc.), the "health", that has led to these different ethnic populations, was the result of the interaction of the particular set of genes that coped with the foods that were available. Today, with the massive diaspora of both people and foods, as well as cultural practices of producing foods, distributing foods, food preparation and consumption of foods, one can see that there is a mismatch of our biologically-derived genes and the rapidly changing cultural practices, particularly associated with nutrition and diets [2-4,62].

Put this in the context of this "Commentary" to try to reduce the risk for childhood cancers via genes and genetic biomarkers in "personalized medicine" [1], there cannot ever be a "universal" nutritional/dietary intervention strategy for one of the greatest ethical challenges we must make. It has been predicted that there might be three billion more babies born before the end of this century and since we would like to reduce the risk to childhood cancers by providing all the potential young mothers of the world to have the best nutritional/dietary opportunities, the best physical environment (clean air/water) and the best psychological, social and behavioral environments for them during pregnancy, the access to the best science is only one of the challenges. The biggest challenges to provide the best total in utero environment are political, economic and ethical. Therein resides the greatest hurdle. First, not all pregnant women are genetically or phenotypically identical. There will be no one nutritional or dietary standard for the whole gestational period. Second, each culture will determine its political framework for providing its economy. Therefore, whether or not each woman has equal access to the funds to get the best nutrition or prenatal health care for her set of genetic/epigenetic components depends on the political decision of that society. Therefore, making any political/economic decision, every culture brings to bear different cultural ethical values. This seems to be the fundamental basis for what Thomas Friedman noted is another collision that is occurring at the same time the biological and cultural evolution is responsible, in large part, for our "metabolic diseases". It is the crisis between "physical technological" changes that are creating "social technological" problems [63]. These new technological options are undermining long held cultural world views in the minds of everyone. This creates a "psychic vacuum" or a world view with a "black hole", where there is either no longer a "moral compass "for making appropriate value decisions or making these decisions on outmoded world views that are non-adaptive for short or long term quality of life consequences [64,65]. It is here that, while science and technology can help to find solutions, the decisions to use or not use those solutions are value and ethical decisions. While these value and ethical decisions cannot be derived from science, as Van R. Potter noted, they cannot or should not ignore scientific facts [66-68]. Given the vast differences in global cultural values but shared biology on the causes of childhood cancers, the solution to the prevention of childhood cancers will remain a difficult solution to be solved.

The idea that traditional philosophical and religious ethical values can inform health decisions can never be universally applied in a pluralistic world. The recent emergence of the concept of "bioethics", which, to most who use the term, is but "warmed-over" medical ethics. Whatever that might mean to a health care professional and his/her patient in Detroit or Cairo, it was never the intension of Dr. Van R. Potter who coined the term [69]. Hence, he coined the term, "Global Bioethics" [67,68,70], to provide a scientific or universal foundation to all human beings living in a global context in a pluralistic cultural world. He never meant it to imply that ethic values could be derived from scientific facts, but rather, no ethical value should ignore scientific facts. That, also, provides more complexities because scientific facts are rarely absolute, but mostly, "incomplete", but correctible.

Therefore, while we know very little about how to maintain the uterine environment to be the best for each women/fetus or for each stage of development, that scientific knowledge must be to focus on how to reduce the risk for childhood cancers. In addition, a greater sensitivity to how we can provide a better total environment for all potentially pregnant women must be one of the obligations of all health care professions. As Van R. Potter stated in his American Association for Cancer Researchers Presidential address: "*Humility with Responsibility: A Bioethic for Oncologists*", [71], we must devote more of our creative energies to use our scientific tradition of always seek-

ing the truth to help reduce needless human suffering, especially to children. Therefore, while it is important we use our love of science and our expertise in any cancer research discipline, we must look at the bigger picture and use that knowledge in the political arena to prevent, as well as treat, childhood cancers.

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