Chapter 1 Introduction

An earlier book I wrote entitled, ***Learning About Your Genes. A Primer for Non-Biologists*** informs readers that our **genes** are made of a chemical entity called **D**eoxyribo**N**ucleic **A**cid, commonly abbreviated as **DNA**, an acronym known to most, if not all, Individuals. In addition to other functions, genes direct the synthesis (manufacture) of the hundreds of proteins that are required for the myriad functions in our cells. You would certainly benefit from reading ***Learning About Your Genes*** before reading ***this book***. That being said, such preparation is not essential for your comprehension of ***Fixing Your Damaged and Incorrect Genes***.

As you will hopefully glean from your reading, fixing damaged and incorrect genes is generally referred to as **DNA repair**. DNA repair is a collection of processes by which a cell identifies and corrects damage to the DNA molecules that reside in all your cells (with the exception of red blood cells, which do not carry DNA), or for that matter any other molecules that reside in the nuclei of other cells.

Both normal metabolic activities and environmental factors such as radiation can cause DNA damage that can result in as many as **a million individual molecular lesions per cell per day**. (A lesion is any damage or abnormal change in the tissue of an organism, usually caused by disease or trauma.

The word is derived from the Latin *laesio* meaning "injury." Lesions can occur in plants as well as animals.

Many of these lesions cause structural as well as chemical damage to the DNA molecule that can alter or eliminate the cell's ability to function normally, principally in the synthesis of the many hundreds of proteins in the cells in your body. DNA damage can also affect the survival of daughter cells that are generated when cells undergo division to generate new cells. DNA repair is consequently constantly active as it responds to damage of the composition and/or structure of DNA. The extent to which cells that have sustained DNA damage can undergo repair is vital to the integrity and function of their genes and thus to the normal functionality of the affected organism.

The efficiency of DNA repair is dependent on many factors, including the cell type, the age of affected cells and the chemical environment outside cells. A cell that has accumulated a large amount of DNA damage, or one that no longer effectively repairs damage to its DNA, can enter several possible states, including **senescence** (an irreversible state of dormancy), cell suicide (known as **apoptosis** or **programmed cell death**), and **unregulated cell division,** that among other complications can result in the appearance of tumors.

DNA damage due either to environmental factors or abnormal biochemical processes that transpire inside cells, has been estimated to occur at a rate of 10,000 to 1,000,000 molecular lesions (damaged molecules) per cell per day. While this constitutes a tiny fraction of the human genome's approximately 6 billion bases (crucial chemical entities in DNA explained in the next paragraph and in a later chapter on the composition and structure of DNA), unrepaired lesions in critical genes such as

those that functionally subdue the formation of tumors (called **tumor suppressor genes**), can impede a cell's ability to carry out its normal function and appreciably increase the likelihood of tumor formation and of various genetic diseases.

The vast majority of DNA damage directly affects the structure of DNA and hence its normal functions. **As discussed in more detail in a later chapter**, DNA contains chemical entities called **bases.** The order and type of the bases (of which there are 4 different types) in DNA constitute a code called the **genetic code**, a code that determines the type and order of amino acids that make up the many hundreds of proteins in your cells, tissues and organs. A simplified explanation of the genetic code and how it works is given in the book ***Learning About Your Genes — A Primer for Non-Biologists*** mentioned earlier.

Many types of DNA damage result in chemical modification of the DNA bases. These modifications can in turn disrupt the structure (and function) of the many genes contained in DNA by introducing abnormal chemical bonds or bulky adducts (chemical additions). The multiple types of damage that cells can be afflicted with are summarized in the following paragraphs.

DNA damage can be subdivided into two main types: **endogenous damage** such as attack of chemical components of DNA by molecules produced during normal metabolic processes or errors generated when DNA is copied, or **exogenous damage** such as that caused by external agents such as ultraviolet radiation from the sun, other types of radiation (including X-rays), certain plant toxins, various human-made chemicals, or viruses.

Tumor suppressor genes (also called antioncogenes) **encode genes** that make proteins called **tumor suppressor**

protein that **help** control cell growth. Mutations (changes in DNA) in **tumor suppressor genes** may lead to tumors. Tumor suppressor genes are normal genes that slow down cell division, repair DNA mistakes, or inform cells when to die (a process known as **apoptosis** or programmed cell death). Multiple tumor suppressor genes have been identified as being responsible for hereditary cancer.

Consider endogenous damage generated in DNA when that molecule is copied. When cells divide, thereby generating new cells during the growth of organs and tissues as a tiny embryo grows to become a fetus, then a newborn infant, and eventually a fully grown person, DNA molecules are copied by a particular enzyme, a process referred to as **DNA replication**. New cells also arise at any age during the healing of wounds, and to replace the loss of cells that occur normally, a good example being the loss and replacement of skin cells and the cells lining our intestines.

A great many biochemical reactions in our bodies are supported by a special class of proteins called **enzymes** that act as catalysts of the biochemical reactions. The replication of DNA to generate new DNA molecules is supported by an enzyme called **DNA polymerase**, which uses each of the **two strands** of the existing DNA molecule as templates. **RNA polymerase** copies a **single** stand of DNA and generates a single-standard RNA molecule. Most enzymes, including DNA polymerase, are highly accurate in the reactions they catalyze. During DNA replication the newly synthesized DNA is chemically identical to the DNA molecule copied by the enzyme. However, no enzyme that we know of is one hundred percent error-free and occasionally mistakes are made during the process of DNA replication such that the chemical structure of the DNA is altered. (Your understanding

of DNA replication and how mistakes during process transpire will be significantly enhanced in a later chapter.)

The rare mistakes that arise during DNA replication are called **mutations**. Mutations can affect the normal functions of genes. However, not all mutations have negative effects. Notably, mutations are the raw material of the genetic variation essential for evolution. Additionally, some mutations may have no demonstrable effect on the health or functions of the bearer of such DNA, in which case they are referred to as **silent mutations**. You, me and all other life forms on planet earth likely carry numerous silent mutations, some of which may distinguish one person from another, in which case they are referred to as **DNA polymorphisms**.

Whereas a mutation is defined as any change in a DNA sequence that is abnormal (implying that a normal version is prevalent in the population and the mutation changes this to a rare and abnormal variant that may or may not alter the normal function of a gene), a polymorphism is a DNA sequence variation that is common in a population but has no functional significance. Polymorphisms are therefore useful for genetic studies in populations, a topic that is beyond the province of this book.

In addition to replication, DNA normally undergoes other biochemical activities. A notable example, during which two DNA molecules exchange segments of any length, is called **genetic recombination**. DNA recombination involves the exchange of genetic material either between multiple chromosomes or between different regions of the same chromosome. This process is generally mediated by homology; i.e., identical or very similar regions of chromosomes line up in preparation for exchange, and some degree of sequence identity is required.

The importance of genetic recombination for the purposes of this discussion on DNA repair, relates to the fact that mistakes during recombination can also alter the normal structure and function of DNA and are a significant source of DNA damage.

In summary, errors in normal DNA function, either during its copying or during its exchange with other molecules, can result in mutations, a prominent source of naturally occurring DNA damage, in this case "damage" defined by incorrectness in the sequence of bases in a DNA molecule.

Up to this point we have been considering examples of **endogenous DNA damage**, i.e. damage produced without an external cause. But components of DNA molecules may also interact with multiple environmental factors such as ultraviolet (UV) radiation from the sun (and more recently from tanning machines) and particularly with a great many chemicals that have an affinity for DNA. All these events consist of **exogenous** sources of **DNA damage**.

X-rays are another potent source of DNA damage, in this case an exogenous damage. X-rays have been used in clinical medicine and for experimental purposes in physics since their discovery in 1895. But their value to genetics research only became apparent when Hermann Muller, an American geneticist, employed radioactivity to produce mutations in the fruit fly *Drosophila*.

Hermann Muller was a member of a research team at Columbia University who, under Thomas Hunt Morgan, an American evolutionary biologist, geneticist, embryologist, and science author who won the Nobel Prize in Physiology or Medicine in 1933 for discoveries elucidating the role that the chromosome plays in heredity, was interested in the physical

and chemical nature of genes. As a consequence, he designed experiments to test the idea that radioactive particles might affect genes and lead to altered genes (mutations).

Beginning in late 1926, while at the University of Texas, Muller subjected male fruit flies (of the species ***Drosophila melanogaster***, a frequently used organism for genetic studies) to relatively high doses of radiation and mated them to virgin female fruit flies. In a few weeks time he was able to artificially induce more than 100 mutations in the resulting progeny — about half the number of all mutations discovered in *Drosophila* over the previous fifteen years! Some mutations were deadly. The effects of other mutations were visible in the offspring but not lethal. As Muller interpreted his results, radioactive particles passing through the chromosomes randomly affected the molecular structure of individual genes, rendering them either inoperative or altering their chemical functions.

Fig. 1.1. Thomas Hunt Morgan.

Fig. 1.2. Hermann Muller.

Muller's insight into genes as individual molecular units was provocative and influential. His research in the artificial genesis of mutations (**mutagenesis**) led to the development of the discipline of molecular biology, a complex and varied topic in biology examined by numerous scientists around the world. In 1946 Hermann Muller received the Nobel Prize in Physiology or Medicine.

The Nobel Prize, in the wake of the atomic bombings of Hiroshima and Nagasaki, focused public attention on a subject Muller had been publicizing for two decades — the dangers of radiation. In 1952, nuclear fallout became a public issue as more and more evidence had been leaking out about radiation sickness and death caused by nuclear testing. Muller and many other scientists pursued an array of political activities to defuse the threat of nuclear war.

When exposed to X-rays that emit **ionizing radiation** (IR), DNA can sustain damage due to breakage of the two strands

of DNA, an event called **double strand breaks (DSB)**. Double strand breaks are considered the most dangerous of all DNA damage. If left unrepaired, the resulting chromosome discontinuity often results in cell death. Fortunately, this form of DNA damage is rare since there are no natural sources of ionizing radiation (IR). But its ability to seriously damage DNA is often used to kill cancer cells. Indeed, IR is an effective and commonly employed treatment in the management of some human malignant tumors. Since the ability of IR to control tumors mainly relies on DNA damage, the cell's DNA damage response and repair processes may sometimes hold the key to determining a tumor's response to radiation.

In summary, alterations of the chemical composition of DNA and/or its normal function that occur for any reason, be it a consequence of faulty DNA replication, faulty recombination, or exposure to environmental agents that interact with DNA, are collectively referred to as DNA Damage.

Fortunately for you, me and all the other living creatures (including plants), biochemical mechanisms for correcting damage to DNA emerged during biological evolution. Had the phenomenon of DNA repair not evolved our planet would likely be bereft of life forms! **These mechanisms, collectively referred to as DNA Repair, are the topic of this book.**

As stated in the introduction to ***Learning About Your Genes,*** "like most intellectual disciplines, biology is a vast field with a vast vocabulary, making it difficult (sometimes impossible) for non-biologists to understand much, if anything, about topics such DNA **R**eplication, DNA **R**ecombination and DNA **R**epair (the three **R's** of DNA metabolism). However, in my considered view there is no *a priori* reason why the vocabulary

of biology cannot be translated into common English that any reasonably intelligent reader can comprehended."

Fixing Your Damaged and Incorrect Genes was written to address that goal. Accordingly, I have strived to convey biological concepts and explanations about DNA repair in terms that non-biologists can readily comprehend, emphasizing key words in bold type — essentially, to inform you about **DNA repair** in plain English. Additionally, while in this day and age most people with computers are experienced in "goggling" words and even phrases they are unfamiliar with, based on my own experience explanations from **Google** can sometimes be curt and frustratingly uninformative. In an effort to address this potential problem, the end of the book presents a **glossary** of key words and terms that I hope you will use if needed. While In this regard the glossary includes the names of the many scientists mentioned in the book, information about these individuals is something that Google usually handles in an informative manner.

The study of DNA and genes, including their repair when damaged or compositionally incorrect is part of an intellectual discipline called **genomics** (a topic that deals with the structure and function of genes, including the repair of damaged or altered genes). Genomics is a discipline that is formally distinct from a more familiar subject that you have presumably heard or read about, called **genetics**, a topic focused on the study of **heredity**, essentially how characteristics of living beings are inherited from one generation to the next. However, **genomics** and **genetics** are closely related topics, both words being derived from the Greek *genno*, meaning, "to give birth."