

Review Article

From Mutagenesis to Metastasis: A General Description of Cancer Development

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Submitted: 06 December 2018

Accepted: 19 December 2018

Published: 20 December 2018

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Keywords

• Cancer; Mutagenesis; Carcinogenesis; Tumorigenesis; Angiogenesis; Metastasis

Abstract

Cancer is known as a set of diseases that, when the prognosis is not favorable for the patients, it ends in death. Clinically three phases of cancer have been described: initiation, promotion and progression. In this context, the molecular involvement in these phases is described: first, the single or multiple mutations at DNA trigger cell transformation; the second step refers to the process of tumor growth, and the latter to the invasive process. Although these terms are well known, molecular processes following a specific order within each of these three phases are explained: mutagenesis, carcinogenesis, tumorigenesis, angiogenesis, and metastasis. Severe mutations commit a healthy cell to transformation, becoming therefore in a cancerous cell with altered metabolism and being able to proliferate unlimitedly to form a tumor mass. This tumor increases its size and stimulates the vascularization for nutrition. At the end of the process, individual cancerous cells escape towards new tissues, making it difficult their localization and compromising vital functions.

INTRODUCTION

Genetic damage that initiates in a normal individual cell drives towards into an abnormal cell in order to originate a carcinogenic process, followed by the growth of a solid tumor mass. Different types of solid tumors are well described: sarcomas, carcinomas, and lymphomas [1]. In case of leukemia, it generally does not form a solid mass; however, it generates an extensive quantity of abnormal cells representing an important clinical impact in population, especially in children, due to its aggressiveness [2,3]; therefore, single mutations or an extensive DNA damage are crucial for cell transformation or the carcinogenic process [4-6]. In this description, carcinogenic process is characterized by the deregulation of normal cellular metabolic pathways disrupting mainly both cell cycle arrest and programmed cell death (PCD) such as apoptosis, autophagy, and necroptosis [6-8], inducing consequently a cell reprogramming [9]. These events, added to epigenetics, result in drug resistance [10-12].

Under normal conditions, the balance between cell proliferation and cell death remains tightly regulated to ensure tissue homeostasis [13,14]; however, this balance could be disturbed after alterations in cellular metabolism. Hence, the first step for cell transformation, and therefore for cancer development, is mutagenesis (Figure 1). As a result, oncogenes become activate, while tumor suppressors genes are silenced or their expression is blocked [9,13,15], this process is described as carcinogenesis. The rapid and uncontrolled proliferation of these abnormal cells converges in benign and/or malignant tumors [8], step corresponding to tumorigenesis. In general, benign tumors do not spread to distant places or invade other tissues.

Usually, these tumors do not possess a threat to life unless they compress vital structures or have some physiological activity (*i.e.* they are able to produce some hormone or proliferative ligand); however, there is evidence that a benign tumor can become in a premalignant tumor and finally becoming malignant [16,17]. The next requirement is the tumor nutrition and growth, facilitated by new blood vessels formed to the tumor mass, process known as angiogenesis; however, this event plays a double role, accelerating the spread of cancer cells to other parts of the body. Therefore, malignant cells invade other nearby or distant organs, process known as metastasis [18-20].

GENERAL CLASSIFICATION OF THE DIFFERENT PHASES OF CANCER

According to several clinical descriptions, cancer development could take three different phases: initiation, promotion, and progression (Table 1) [21]. Within these phases is possible to describe the characteristics acquired by cancer cells from the induction of mutations (mutagenesis) to the spread of cancer cells (metastasis). Likewise, the period of each of the phases varies; this is according to the cell type affected and the microenvironment where the cancer is originated.

INITIATION

In this phase the initial process of DNA damage is described. Mutations of genes involved in cell proliferation such as proto-oncogenes, tumor suppressor genes, genes related to genome stability, and genes involved in cell signal transduction, are responsible for the initiation of the carcinogenic process [9,15]. Cells lose their normal biological and morphological

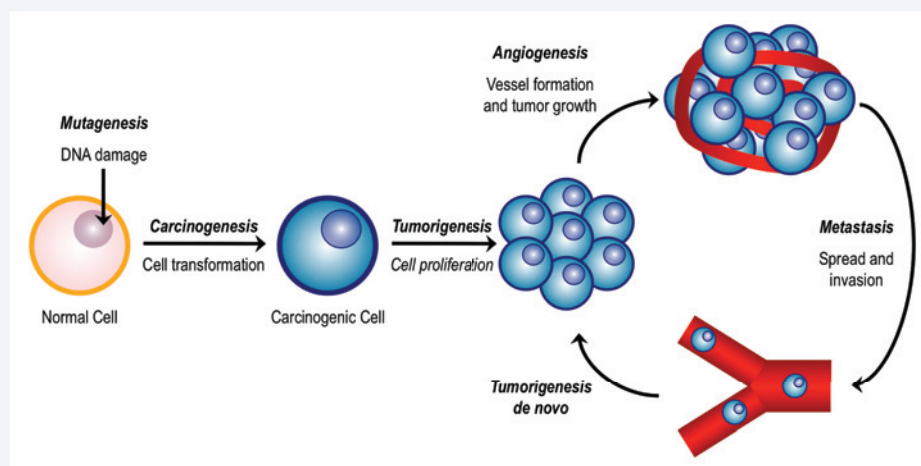


Figure 1 Cancer development: DNA damage is induced, normal cell change its metabolism becoming a cancerous transformed cell. Proliferation is uncontrolled until forming a tumor mass; as the tumor grows new blood vessels are formed for nutrient irrigation. Cancerous cells invade other adjacent or distant tissues through the new vessels formed to growth and form a new secondary tumor.

Table 1: Cancer development: distribution of different stages.

Phases	Initiation		Promotion			Progression
Stages	0		I	II	III	IV
Sub-phases	Mutagenesis	Carcinogenesis	Tumorigenesis		Angiogenesis	Metastasis
Time (years)	≈ 5 – 30		≈ 1 – 5			< 1
Description	Presence of abnormal cells with no tumor formation		Abnormal cell proliferation and tumor growth			Tumor cell dissemination

characteristics; becoming into an irreversible process in which the cell is required to attend at least one cell division cycle in order to transmit their damage to the descendant cells [22]. This carcinogenic property depends, in specific cases, on extracellular ligands; for example, cells of the immune system are able to recognize these abnormal cells and, consequently, synthesize signaling molecules that disrupt their proliferation leading them to cell death [23-25] as occurs with senescent cells [26]. Then, within this phase, a Stage 0 is pronounced: mutations in DNA are generated and normal cells are transformed. However, it is not a cancer yet; being therefore dependent on several factors that facilitate the cell reproduction to form a tumor mass and then disseminate elsewhere. In a best-case scenario, DNA damage can be repaired or abnormal cells can be eliminated. If not, abnormal cells continue to the next phases and generate cancer. Therefore, within the initiation phase cells follow two different sub-phases, starting from the DNA damage or mutagenesis, induced mainly by carcinogenic agents, followed by the final result of these mutations, such as the activation of oncogenes and/or inactivation of tumor suppressor genes, transforming a normal cell into a carcinogenic cell, process known as carcinogenesis.

Mutagenesis

All of the cells of the whole body are constantly exposed to different endogenous and exogenous agents that induce somatic mutations in a directly or indirectly manner [5,15,27]. In cellular metabolism, substances such as oxygen reactive species (ROS) or other genotoxic biomolecules, are responsible for cellular

stress, generating the instability of the genome and inducing mutation accumulation. The level of DNA mutations that occur could also depend on the ability of cells to activate the DNA repair machinery; in this respect, six DNA repair mechanisms have been described: base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR); non-homologous end joining (NHEJ), and translesion synthesis (TLS) [15]. DNA repair converges in the induction of cell cycle arrest or activation of apoptosis; in contrast, if any of these different mechanisms are not able to repair the DNA damage cell transformation is inevitable [17].

Several mutagenic agents have been described. They are capable of modifying the DNA sequence; however, it must be considered that not all mutagenic agents are prone to cause cancer [28]; therefore, in a specific manner it is possible to call them as "carcinogenic agents". In general, carcinogens could be chemical, physical or biological agents, being the first one the most abundant and responsible for most types of cancers [29]. Moreover, epigenetics is also involved in cancer development because chemical modification of gene expression by methylation and post-transductional modification of histone proteins have been identified in certain types of cancer [9,10,30].

Carcinogenesis

After the generation of several DNA mutations, cells respond to changes in the metabolism according to the new information received. The carcinogenic process is the transformation from a normal cell to a potentially carcinogenic cell [6]. At this

point, two groups of proteins are involved: oncogenes and tumor suppressor genes. Oncogenes are originated from proto-oncogenes, which encode all the proteins that facilitate cell growth, migration, division, and differentiation, in a normal and regulated manner. The mutations that affect this group of genes result in the activation of their carcinogenic form, oncogenes, providing unlimited unregulated dynamism and they stand out for their high expression or constant activation; this is the case of *RAS* and *MYC* oncogenes, expressing oncoproteins with unlimited activity, facilitate abnormal cell proliferation and immune system evasion [12,23,25,31,32]. On the contrary, tumor suppressor genes express proteins that stop or inhibit cell cycle progression, cell development, and cell differentiation, in addition to activate cell death processes. Mutations suffered in these genes result in a poor expression, repressed expression or functional inactivity of proteins to inhibit proto-oncogenes or active oncogenes such as *RAS*, *MYC*, *E2F*, etc. [8,13,23].

A good example of tumor suppressor gene is p53 (Figure 2). Briefly, after oncogene activation or DNA damage, ARF and ATM/ATR (ataxia telangiectasia-mutated/ATM and RAD3-related) pathways become activated, respectively. ARF induces MDM2 (mouse double minute 2 homolog) phosphorylation being inactivated. MDM2 plays a fundamental roll in p53 regulation: in normal conditions MDM2 downregulates p53 through ubiquitination to promote cell cycle for proliferation and differentiation. In cancer cells, MDM2 oncoprotein forms a tight physical complex with p53, thereby inhibiting p53-mediated transactivation events [21]. In contrast, ATM/ATR induces Chk1/2 (Checkpoint kinase 1/2) transactivation to activate p53 [33]. Once p53 is activated it participates in different pathways involved in the correct functioning of the cell. Contrary, in the absence of p53, angiogenesis is stimulated and cancerous cells are able to avoid cell cycle arrest, DNA repair, cell differentiation, and PCD.

Alterations in one or both groups of genes provides an imbalance in the different cell metabolic pathways supporting

several processes as cell division, tumor growth, and cell migration [4,5,12,30,34-36]. It has been well reported that a large percentage of cancers are due to mutations in p53 gene and, as a result, its protein is not present or its synthesis and function are obsolete, generating DNA damage accumulations and preventing its repair, cell cycle arrest is inhibited and the apoptotic process is not activated [4,5,34,37]; therefore, a cell with mutations in the p53 gene is easily converted into a cancerous cell. It has been also demonstrated that p53 is involved in autophagy and other cell death pathways [35]. All these discoveries reveal the impact of p53 not only on the activation of autophagy cell death pathway, but also in surviving; in basal conditions, cytoplasmic p53 inhibits autophagy, thus allowing cell surviving; while nuclear p53 activates autophagy in starvation conditions downregulating themTOR (mammalian target of rapamycin) protein, an inhibitor of this pathway [38]. Further, p53 destabilizes the Bcl-2-BECN1 complex through phosphorylation and inactivation of Bcl-2; once BECN1 is released, the autophagic processes is activated [32,35,37]; even more, the pro-autophagic proteins LC3-II and DRAM were demonstrated to be downregulated after p53 silencing in human tumor cell lines [39].

To note, not only mutations in the p53 gene, or other proteins involved in cancer progression, are responsible of cancer development. Proteins encoded from exogenous genetic material, mainly viral DNA [40], are able to inhibit or modulate the function of these proteins. A well-known example is the Human Papilloma Virus (HPV), which encodes a protein called E6; this viral protein causes p53 inactivation within the ubiquitin proteasome pathway [36,41]. In summary, both endogenous and exogenous carcinogenic agents, induce cell transformation, causing thereby the origin of cancer. The study of the activation and overexpression of both oncogenes and anti-apoptotic proteins have been in fact a key to develop new anticancer drugs, in order to reduce or block their activity [12,42].

PROMOTION

Several processes are involved in the promotion of cancer

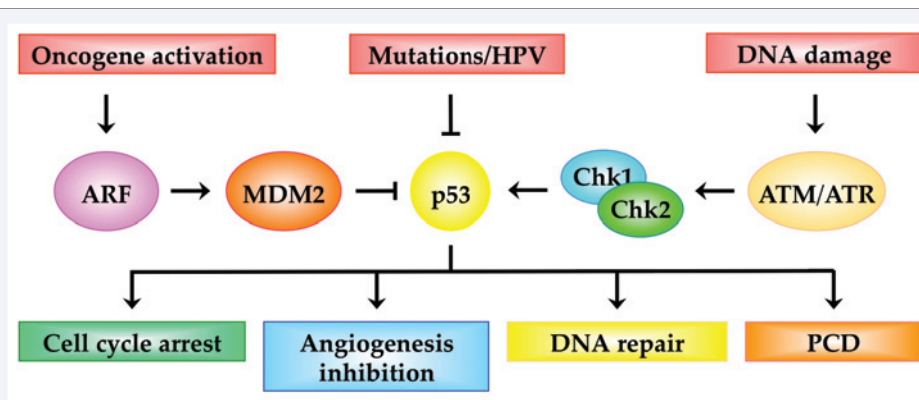


Figure 2 p53 main functions: the active form and overexpression of p53 is observed under the presence of active oncogenes and DNA damage. Many functions are regulating by this protein: cell cycle arrest, senescence induction, angiogenesis inhibition, DNA repair, and apoptosis activation. More than 60% of cancer shows at least one mutation in p53 gene, encoding a non-functional protein or deleting its expression. On the other hand, oncoproteins belong from viruses such as HPV could inactivate p53 protein through ubiquitin proteasome pathway.

Abbreviations: HPV: human papilloma virus;MDM2: mouse double minute 2 homolog; Chk1/2: Checkpoint kinase 1/2; ATM/ATR: ataxia telangiectasia-mutated/ATM and RAD3-related; PCD: programmed cell death.

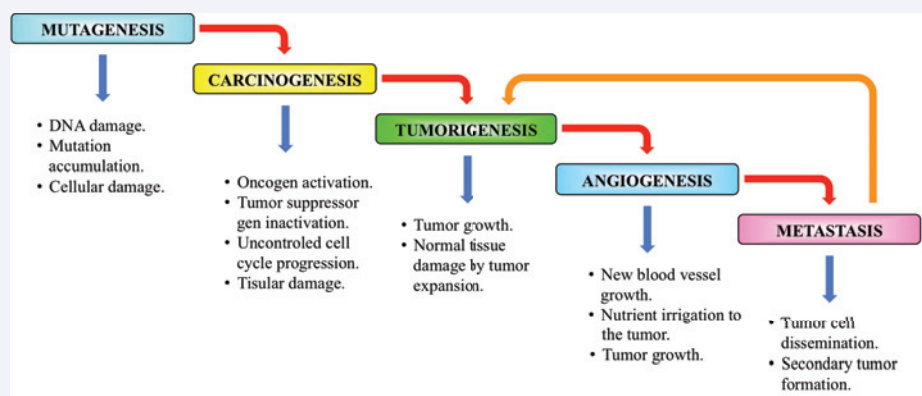


Figure 3 Sub-phases of Cancer. General descriptions of the different aspects that cancer cells take since mutations are generated at the DNA level (red arrows). In addition, a repetitive cycle is indicated between tumorigenesis and metastasis. When secondary tumors are formed a new repetitive cycle is taken (orange arrow).

and the deregulation of cell death after cell transformation [35], furthermore, many hallmarks of cancer have been described, these are: sustaining proliferative signaling, evading growth suppressors, resisting cell death and avoiding immune system, among the most important [43]. All these events promote uncontrolled cell proliferation, stimulating therefore tumor development or neoplasia. As tumors growth or expand they require new nutrients; therefore, tumor cells get their nutrients from neighboring cells [25,44] or generate signaling mechanisms. In this context, cancerous cells stimulate the proliferation of epithelial blood vessel cells in order to form new blood vessels towards the tumor, allowing therefore its growth [19,45]. This sub-phase is well known as angiogenesis, an active normal process in embryogenesis and in certain cases such as tissue regeneration, although it is also involved in cancer promotion. Another interesting mechanism of surviving is the activation of the autophagy pathway, playing therefore a double role after its activation, generating enough nutrients for cancer cell surviving without killing these abnormal cells [32,37,44,46,47].

Clinically three stages have been determined within this phase: Stage I, where the cells barely transformed begin to divide until they have a large size or cell number is abnormal; although it is still small (solid tumors up to 2cm in diameter), it can already be detected. In the next Stage II, the tumor has grown into a considerable size (solid tumors up to 5cm in diameter) or the number of abnormal cells has exceeded the normal ranges being easily detectable [48]. Therefore, up to this point, cancer cells are in the sub-phase of tumorigenesis and, in order to continue its proliferation, they require new nutrients. This requirement is given in a beginning manner by itself through autophagy pathway activation [32,37,46] and following by the induced angiogenesis, considered into the Stage III, where the tumor with sufficient nutrients, facilitated by the new blood vessels formed, grows beyond 5cm in diameter and expand towards adjacent tissues [48].

An important characteristic in certain tumors is the requirement of a determined time for the induction of angiogenesis. This time that can be used by immune system to take charge of the elimination of the malignant cells or the tumor

mass [23-26]. On the other hand, the early detection of localized small solid tumors facilitates their surgical extirpation before the angiogenic or metastatic processes, the latter corresponding to the next phase.

Tumorigenesis

When genetic and microenvironment conditions are favorable for a cancer cell to proliferate indefinitely is when the tumorigenic process begins; to note, most solid tumors are heterogeneous with respect to cell proliferation and differentiation [49]. Tumorigenesis is nothing more than the tumor growth until it reaches a considerable size that could change the organ normal functions from which it is originated. In this phase, two types of neoplasia are generated: benign and malignant. The first one is enclosed in a membranous and fibrous capsule, while the second is not. In both cases, without barriers arresting the tumor growth, cancerous cells continue its proliferation and spreading [50]. There is also a process of tumor expansion, compressing and consequently causing injuries on the adjacent organs. In addition, for tumor expansion, it is necessary to eliminate any tissue or organ that prevents such growth. In this way, tumor cells have the ability to synthesize and secrete digestive enzymes such as metalloproteases, which consist in a group of enzymes with proteolytic activity. The main one involved in the development of the tumor (and its spread) are the Matrix Metalloproteinases (MMPs), whose function is to degrade the extracellular matrix (ECM) [51,52]. The principal target of MMPs is collagen IV, a major component of the basement membrane (BM) [51,53]. The degradation of collagen IV promotes tissue dismantling and therefore tumor invasion. This mechanism could also facilitate the angiogenic process.

Angiogenesis

The term angiogenesis refers to the growth of new blood vessels from those pre-existing. Under physiological conditions, angiogenesis is activated in response to tissue damage; stimulating the formation of new blood vessels in order to prevent severe damages caused by the lack of nutrients such as hypoxia [19,30]. In case of cancer, angiogenesis promote tumor growth [54,55]; therefore, cancer cells synthesize and secrete growth factors such

as Vascular Endothelial Growth Factor (VEGF), which, through their specific receptors present in blood vascular epithelial cells (VEGFR), stimulate cell proliferation towards malignant tumor. In this way, new blood vessels carry nutrients to the tumor formed, promoting not only its growth, but also its dissemination to distant places in the body [30,45,55,56]. Although a large number of tumors are able to spread without angiogenesis; the need for nutrient supply is important for tumor growth and, as reported by Folkman in 1989 [20], angiogenesis facilitates metastasis; allowing therefore the progression of cancer.

PROGRESSION

In this late phase, it is most likely that the tumor or cancerous cells have spread to different parts of the body, near or distant from the initial tumor [18]. This process of dissemination is called metastasis, the last sub-phase, which could be facilitated by previous angiogenesis [18,19,54,55]. Cancerous cells spread through the new-formed blood vessels are housed in new tissues to initiate a new tumorigenic, angiogenic, and metastatic process; in conclusion, they form a repetitive carcinogenic cycle. Thus, new tumors grow throughout the body, making it difficult to localize and treat them in order to eliminate all solid tumors formed [57]. This phase has also been cataloged within Stage IV of cancer and the patient life expectancy is very low.

Metastasis

Metastasis has been responsible for a large number of deaths due to the spread of individual cancerous cells that detach from primary tumors. These abnormal individual cells proliferate in different places obstructing the function of the still functional organs [18,57]. It is important to note that in some cases a previous angiogenic process is not required to promote this invasion; it is enough to only disaggregate the extracellular matrix (by MMPs); therefore, abnormal cells could be directed to new places in the organism [51]. To promote migration, either through adjacent healthy tissues or neighboring blood vessels, tumor cells modify their cytoskeleton and anchor to the ECM or to other cells surface by means of integral proteins of membrane that are expressed over these cells [2,35]. Type IV collagen is found at the basal surface of epithelial and endothelial cells and is essential for tissue polarity; facilitating not only cell migration and invasion of carcinogenic cells, but also angiogenesis [53]. Moreover, chemokines, acting as a chemoattractant to guide the migration of cells, play a crucial role in tumorigenesis and metastasis; therefore, within a tumor microenvironment, CCL2 (C-C motif chemokine ligand 2) and other ligands, secreted mainly by tumor-associated macrophages (TAMs) and fibroblast, adjacent to the tumor, promote the migration of several cancer cell types [58]. Several microRNAs have been also involved in metastasis, including EMT (epithelial-mesenchymal transition), due to the conversion of adherent epithelial cells to mesenchymal cells, being capable to migrate to other tissues [18,52,59,60]. Even more, in mouse models with E-cadherin knockout, tumor progression and metastasis were observed, suggesting that the loss of E-cadherin is crucial for cell migration and invasion [61].

As previously explained, cancer cells have the capability to avoid cell death stimulus such as apoptosis; however, cancerous cells traveling through the bloodstream have to be able to survive

in an environment where immune system is active. It is well known that a correct immune response allows the recognition of tumor cells; being therefore easily recognized by macrophages that, once they identify these abnormal cells, activate the apoptotic cell death pathway. In this way, the immune system would prevent the proliferation, spread or invasion of abnormal cells [23-26,51]. Nonetheless, to confront this inhibition of metastasis, the tumor cells synthesize the Tissue Factor (TF) [57]; a glycoprotein capsid expressed in fibroblasts, endothelial cells of blood vessels, and monocytes. Physiologically TF is absent, but when an injury occurs (rupture of a blood vessel) its presence is essential to start the coagulation cascade. Therefore, when a tumor cell enters the blood vessels it presents TF, recruiting platelets that surrounding the tumor cell for protection [62,63]. The platelets then form a shield that prevents contact with surrounding macrophages until reaching the site of invasion. TF stops their expression when the tumor cells pass from blood into tissues; therefore, the shield formed by platelets disintegrates [57].

Once the tumor cell is lodged in the new tissue, the process of tumorigenesis begins again, this process is described as tumorigenesis *de novo* (Figure 1, 3); consequently, the initial tumor cell will divide until forming a new tumor mass that affects the invaded tissue. A new angiogenic process will be activated in order to promote the metastasis of this secondary tumor [19,55]. This process will follow several repetitive cycles in which new tumors develop in different parts of the body from previously formed; final process of progression phase, where patients are less likely to survive.

DISCUSSION AND CONCLUSION

The origin and development of cancer occurs gradually and orderly in different sub-phases in which each depends on the previous one. Cancer cells are generated from the induction and accumulation of several DNA mutations: Mutagenesis; followed by cell transformation: Carcinogenesis [6]. The different DNA mutations cannot necessarily cause a cancer; since, whether the DNA repair machinery works properly the damage can be repaired and the cell continues with its normal metabolism; or mutations provide a sufficient level to be able to adapt to the environment or to evolve. Thus, in this context mutagenesis is discussed separately from carcinogenesis. Carcinogenesis includes the activation of the oncogenes and/or the inactivation of the tumor suppressor genes after DNA mutations, causing an antiproliferative processes evasion and obey an uncontrolled replication. Nevertheless, when a cancerous cell enters in this sub-phase does not mean it ends in cancer because an effective process of cell death and the immune system could recognize these cells with metabolic disorders to induce them to a PCD [23,24]. Deficiency in cell death activation (*i.e.* apoptosis) or failures in the immune system, as occurs in immunosuppressed condition, carcinogenic cells continue in the next sub-phase: Tumorigenesis, where cell division has no control; consequently, they proliferate uninterrupted to form a tumor mass. All the cells of this tumor mass contain the same genetic characteristics and are potentially cancerous.

To promote tumor growth, cancerous cells feed themselves through autophagy; however, the induction of new blood vessels growth around the tumor is activated in order to nourish it,

this process is known as: Angiogenesis. The new blood vessels formed play a double role in the progression of cancer: feed the tumor accelerating their proliferation and on the other hand they facilitate the spread of tumor cells to distant places: Metastasis. This is the final step of a repetitive cycle of cancer development (Figure 1); when cancer cells become independent of the primary tumor, they travel to lodge in a new space of the organism and form a new tumor mass (tumorigenesis) and therefore, to continue a repetitive cycle generating new tumors. Finally, not all types of cancers act in the same way; however, most of these follow the same pattern explained above, in this context, it is important to know each of the molecular mechanisms involved in the carcinogenic process in order to understand the behavior of cancer development.

ACKNOWLEDGEMENTS

I thank the Universidad Técnica Particular de Loja for support this review.

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Cite this article

Guamán-Ortiz LM (2018) From Mutagenesis to Metastasis: A General Description of Cancer Development. *J Cancer Biol Res* 6(3): 1123.