

## Depleted uranium induces human carcinogenesis involving the immune and chaperoning systems: Realities and working hypotheses



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### ABSTRACT

Cancer is caused by a combination of factors, genetic, epigenetics and environmental. Among the latter, environmental pollutants absorbed by contact, inhalation, or ingestion are major proven or suspected culprits. Depleted uranium (DU) is one of them directly pertinent to the military and civilians working in militarized areas. It is considered a weak carcinogen but its implication in cancer development in exposed individuals is supported by various data. Since not all subjects exposed to DU develop cancer, it is likely that DU-dependent carcinogenesis requires cofactors, such as genetic predisposition and deficiencies of the chaperoning and immune systems. It is of the essence to adopt every possible protective measure as well as performing careful screening for early diagnosis to protect the military that work in war areas in which weapons with DU are, or have been, used. These topics are discussed here, along with a proposed working hypothesis for investigating the pathophysiology of DU-related carcinogenesis, including the possible role of the chaperoning system.

### Introduction

This report briefly summarizes some of the main and most-up-to-date knowledge on the development of malignant tumors, focusing on the impact that exposure to depleted uranium (DU), even for short periods, can have on the health of people at risk, such as military personnel.

#### Tumors

Tumors can be classified into benign and malignant. The latter are one of the main causes of death worldwide, but especially in populations with a better standard of living [1]. One of the reasons for this preference may be that people living in poor condition are more immediately confronted with health risks other than those that are carcinogenic, for example malnutrition and hygienic deficiencies, which often contribute to disease and to the death by infections not adequately treated, before carcinogenesis has had the chance to develop. In contrast, well to do populations living in more “civilized” areas are usually exposed to various types of environmental pollutants, many of which potential carcinogens that can be absorbed through air, water, food, and skin contact.

#### Environmental pollutants and tumors

Environmental pollutants are physical, chemical, and biological agents to which we may be exposed, at different concentrations and for different times, during our life. One of the biggest social problems is pollutant exposure at the workplace, which may be more or less serious depending on the type of work [2]. Among the workplace environmental pollutants there are heavy metals and radiation to which the military can be exposed in war zones [3].

It has been widely debated by the international scientific community which tumors are most likely to develop preferentially in the

military who have served in areas deemed potentially contaminated. The most recent scientific evidence on the causes of tumors, and in particular the combination of genetic (dependent on cell DNA) and epigenetic (dependent on cellular mechanisms controlling the expression of cellular genes and their translation into structurally intact and normally functioning proteins) abnormalities, suggests that various types of neoplasia can be generated by these pollutants, with one of the most important pollutants being DU [4].

#### Carcinogenesis: a multi-step process

The human body is made up of hierarchies: the organs are composed of tissues and these in turn are made of cells. Regardless of the type of tissue (the human ones are divided into four main groups: epithelial, connective, muscular, and nervous), each of them is made up of cells that have similarities and differences, the latter being the result of the differentiation process that undifferentiated resident cells undergo (these cells are often inappropriately called “stem cells”). Therefore, a characteristic that all the tissues have in common is that of possessing undifferentiated cells that from a very high to a very low frequency, depending on the anatomical districts and other biological variables (including stress), divide and begin a differentiation path that will lead them to become differentiated cells.

From the morphological point of view, the presence of undifferentiated cells that proliferate without differentiation is an anomaly that is commonly described with the term “dysplasia” and it is considered a pre-tumoral lesion. From a molecular point of view, the mechanisms that lead to the development of cancer in a normal tissue (the so-called “carcinogenesis”) are many but today there is consensus in the international scientific community about the stages of carcinogenesis (Fig. 1) that can be summarized as follows: 1. Initiation, that is the onset of initial genetic alterations in nuclear DNA that transform the cell from normal to potentially tumoral; 2. Promotion, that is the accumulation in nuclear DNA of further alterations, both genetic and

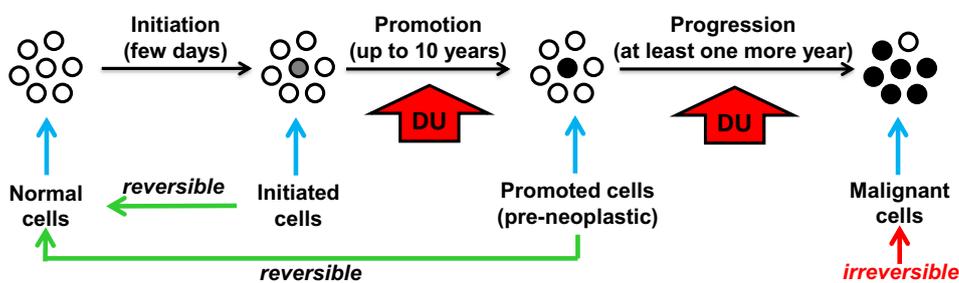


Fig. 1. The three major steps of the carcinogenic process: Initiation, promotion, and progression, and the possible impact of DU. Normal cells become transformed into malignant cells by a process triggered by various factors, genetic and non-genetic (e.g., environmental pollutants). Among the latter, DU can play a determinant role at any one step, particularly in the promotion and progression steps. While the first two steps are reversible and, therefore, amenable to treatment, the last step is not.

epigenetic (the latter generally induced by carcinogens present in the environment), which give these potentially tumoral cells the ability to uncontrollably proliferate without differentiating (dysplasia); and 3. Progression, consisting of subsequent events, for instance escape from the control of the immune system, that give to uncontrollable proliferating tumor cells the ability to invade the surrounding tissues and to metastasize in organs at a distance from the site of tumor onset.

### Natural defense against tumors

The multi-step process outlined above and in Fig. 1 can take a long time, even a few decades, before the tumor becomes clinically evident [5]. The immune system plays an important role in carcinogenesis. Among the circulating immune cells, natural killer (NK) lymphocytes have the ability to identify foci of tumor cells and eliminate them before they invade and proliferate in surrounding and distant tissues [6]. Unfortunately, the immune system is sometimes unable to recognize and/or eradicate the emerging neoplasm, due to quantitative or qualitative defects in immune cells, and the tumor has the chance to progress. In the following paragraphs, we will discuss how exposure to DU may facilitate carcinogenesis, in particular by participating in the promotion and progression steps, through epigenetic alterations and immune system weakening, respectively. We will also introduce the chaperoning system which, like the immune system, participates in protecting the organism against noxae of all kinds but, also like the immune system, can become defective or pathogenic and contribute to mechanisms of disease [7].

### Effects of depleted uranium exposure on the human organism

We have to analyze separately the issues of contamination of the war theaters and the neighboring area and how DU enters and deposits in human body.

#### Contamination

A group of researchers from universities of the former Yugoslavia, a region of the World in which recent wars have caused contamination by DU, has published a comprehensive review that analyzes the current state of knowledge on the effects of DU chemical toxicity and radioactivity on human tissue and organs [8].

The DU that accumulates in the war zones comes from the explosion of weapons containing the metal, which causes the production DU nanoparticles and their release into the air. These nanoparticles can travel with the winds even for tens or hundreds of kilometers before settling in the soil and, carried by rain water, infiltrate the groundwater of the subsoil [9]. This spread of contamination can go virtually indefinitely since DU nanoparticles can have a half-life of billions of years [10].

#### Contact, absorption, circulation, deposition, and pathology

The three main entry routes of DU nanoparticles in the human body are the skin (by contact), the lungs (by inhalation), and the mucosa of the alimentary canal (by ingestion). Once in the circulation, DU

undergoes a series of chemical reactions (formation of oxides, hydroxides, and carbonates) that increase its capacity to accumulate in tissues [11]. As it travels with blood, it is natural that DU deposits preferentially in the most vascularized tissues and organs.

Remarkably, according to a number of studies recently reviewed, even a short exposure to DU can increase the risk of cancer [8]. The underlying mechanisms include epigenetic alterations caused by DU. Among the organs in which the most harmful effects of DU accumulation have been ascertained are kidneys and bones. In the kidneys, DU can cause acute and lethal tubular necrosis.

The bones constitute the skeletal apparatus of the human body. Bone tissue, both spongy and compact, houses bone marrow inside. Bone marrow is the most important hematopoietic organ in the human body. Unlike other organs, it has no territorial continuity but is distributed within all skeletal segments. There are three types of bone marrow: red, yellow, and gelatinous [12]. The first is the active one, where hematopoiesis takes place, and in adults it is concentrated in the bones of the axial skeleton and the main bones of the limbs. The yellow bone marrow is formed in adults by adipose substitution of the red marrow, especially in the bones of the moving parts of the limbs. Yellow marrow can be reactivated and become red, in case of physiological needs or pathological hematopoiesis as seen in various blood diseases. The gelatinous bone marrow is present only in elderly subjects. In the aged yellow bone marrow genetic and epigenetic phenomena, mainly affecting reticular stromal cells, modify the microenvironment of hematopoietic stem cells, making it impossible for these stem cells to be reactivated into hematopoietically active elements typical of red marrow.

The red bone marrow is a highly vascularized organ responsible for producing all the corpuscular elements of the blood (red and white blood cells, and platelets) starting from an undifferentiated cell, the hematopoietic stem cell. White blood cells, or leukocytes, are classified into granulocytes and agranulocytes. The latter include lymphocytes, which in turn are classified into B cells, T cells, and NK cells. The hematopoietic process includes the periodic division of the hematopoietic stem cell: one of the two daughter cells remains as stem cell and the other begins the hematopoietic differentiation process. The latter process firstly involves the acquisition of differentiation capacities along a blood line (e.g., erythrocytes, or platelets, or monocytes), with the formation of a clone of cells not yet differentiated but orientated to differentiate in a determined sense followed by the subsequent differentiation of the clonal cells that, after the acquisition of the mature phenotype, are released into the blood and begin to circulate [13].

The tendency of DU to accumulate in the bone marrow has been demonstrated by both human and animal studies. The accumulated DU in the bone marrow has been associated not only to the onset of specific blood tumors (e.g., leukemias) but also to the reduction of the efficacy of the immune response, especially in qualitative terms and, above all in what concerns the innate immune response in which NK lymphocytes play an important role [14,15].

As reported in the last two publications cited above, in addition to the kidney and bone marrow, DU accumulation also occurs in other organs, including intestine, liver, and the eye, and the reproductive and nervous systems. Hence, no organ can be considered safe from DU

accumulation. Even in an organ like the eye (that is richly vascularized in the intermediate layer of its wall, the choroid), where the development of tumors is a very rare occurrence, DU accumulation can induce epigenetic changes (such as DNA hypermethylation) that can be responsible of tumor development, especially and for unknown reasons in males.

### The inevitability of carcinogenesis

It is now a principle accepted by the scientific community that, during the life span of humans, various neoplasms develop over time which, however, are eliminated by immune surveillance mechanisms before spread and clinical manifestations occur. The accumulation of mutations, as a side effect of the tissue regeneration processes occurring constantly throughout the body, and the reduction of the efficacy of the immune response are at the basis of the progression of incipient tumors followed by clinical symptoms. This silent battle between incipient tumors and the immune system, sometimes favoring the former, emphasizes the need for cancer screening programs so the tumor can be detected early, when the chances of successful treatment are still positive. Another important issue is the chaperoning system and its role in carcinogenesis, as it will be discussed later.

#### Genetic vs. non-genetic factors

In 2015, it was proposed that we get sick of cancer by chance and bad luck [16]. This idea was confronted by those who support the opinion that lifestyle and environmental factors are if not the only at least the main reasons for the onset of cancer. In fact, the controversial study emphasizing chance rather than environment, did not claim to exclude the classic risk factors (smoke, solar radiation, environmental pollution, poor nutrition, etc.) but highlighted the essential role of genetic mutations that are at the basis of the first stages (initiation and promotion) of cancer onset.

Along these controversial lines, another important report appeared in 2017 [17]. This time, the assertions were supported by large amounts of data and were not the target of criticism by the media as much as in the previous occasion. It was clearly shown that DNA mutations depend on random genetic errors that arise during the life of the cells, particularly when they replicate as required by tissue regeneration. These genetic errors happen whatever we do, no matter whether or not we live with very healthy habits in clean environments.

Therefore, according to these reports, not being able to avoid the onset of these mutations that underlie the development of cancer, the only way to defend ourselves from cancer would be to avoid as much as possible exposure to environmental pollutants, including those present in the work place. Also, maintenance of efficient immune and chaperoning systems with healthy diets and hygiene habits can reduce cancer risk.

#### The chaperoning system

The chaperoning system (CS) is currently being recognized as an important multimolecular apparatus essential for protein homeostasis and other key cellular events [18]. The system is composed of molecular chaperones, co-chaperones and chaperone co-factors, and chaperone interactors and receptors widespread throughout the body [19]. The main functional associates of the chaperoning system are the chaperone-mediated autophagy (CMA) machinery, the ubiquitin-proteasome system (UPS), and the immune system. Some of the most studied chaperones are Hsp60 and CCT (also called chaperonins), Hsp70, and Hsp90.

While all the components of the CS have evolved to maintain health, molecular chaperones can also be pathogenic when they are abnormal in structure, or when they are caught in a pathogenic pathway, for example in carcinogenesis. In various examples of carcinogenesis,

chaperones apparently normal, at least as much as it can be determined with currently available technology, help cancer cells to grow, proliferate, and metastasize. The chaperones that supposedly evolved to protect the cell and the organism are, thus, turned against their host organism and this is the reason why these conditions are named chaperonopathies by mistake or collaborationism [20]. It is likely that a “mistaken” chaperone is in fact altered by post-translational modifications induced by pollutants, e.g., chemicals in air, water, food, etc. In this way, any carcinogenic agent (even if weakly carcinogenic like DU) may achieve its pathogenic potential, namely by hijacking chaperones via chemical modification. This is a mechanism that could very well be at play in cases in which DU is linked to cancer development, a possibility that has been already observed [21–23] but deserve further exploration.

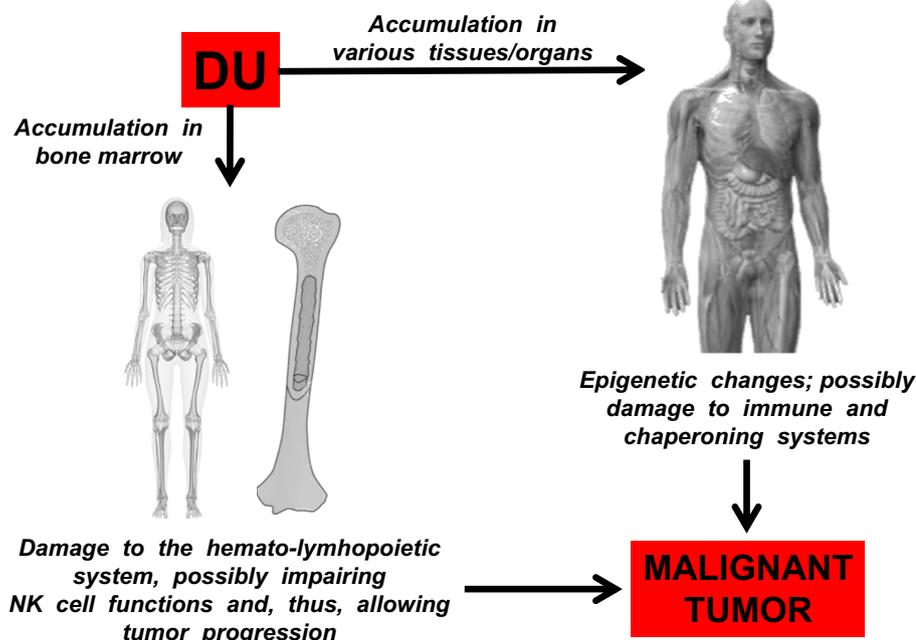
We have also found that there are compounds that can promote post-translational modifications in a molecular chaperone and that the chaperone with the modifications changes its properties and functions drastically [24,25]. The same may be true for DU, which could induce molecular changes in a chaperone and thus enlist it in the set of molecules necessary for malignant transformation and growth.

### DU and carcinogenesis: Can molecular chaperones be the link?

The questions of whether or not DU causes cancer and if yes, with what frequency and under what conditions, are still incompletely answered. Overall, there is evidence in favor of DU as being a weak carcinogen but whether it causes cancer in humans with significant frequency is still debated. Nevertheless, the association of DU exposure and cancer development in humans appears strong in a number of instances. This suggests that although DU is a weak carcinogen by itself it can cause cancer, probably when another factor potentiates its effects and/or when it induces carcinogenesis indirectly by modifying/inducing a molecule that favors cancer development. A candidate for such molecule, that when modified by DU promotes malignancy, could be a molecular chaperone. It has already been shown that DU can modify Hsp70 and Hsp90 (two main members of the chaperoning system) gene expression [21–23]. However, we are far from understanding how these modifications affect the normal cell differentiation process, in turn inducing carcinogenesis. Furthermore, we do not have information about other chaperones in terms of genetic and/or epigenetic modification induced by DU. We propose such a role for chaperones based on what happens in various types of tumors in which one or more molecular chaperones are essential for tumor-cell growth and dissemination. Because of this, treatment strategies are being developed and tested, consisting essentially in negative chaperonotherapy, i.e., blocking the pathogenic chaperone [26]. Maybe a similar approach could be applied to avert the carcinogenic effects of DU. This is why we propose that studies of DU pathogenesis should include investigations of its effects on chaperones known to be crucial for carcinogenesis induced by other agents.

### Is there a causal link between exposure to depleted uranium and human cancers?

In light of what has been reported so far, partly discussed in the preceding Sections of this article, the existence of a causal link between DU exposure and death due to malignancy seems to be supported by various observations, as follows: 1. Virtually all tissues/organs are potential sites of DU deposit, especially the most vascularized ones, because DU travels in the organism through the blood; 2. In the tissues/organs in which it is deposited, DU can induce epigenetic alterations, which can alter the differentiation of cells in two ways: a) cells acquire a correct phenotype but are not functionally efficient (it could be the case of NK lymphocytes); or b) cells lose their differentiation capacity altogether. The latter is a pro-neoplastic event (tumor promotion, Fig. 1) as it increases the likelihood that cells with tumorigenic



**Fig. 2.** Overview of the anatomic distribution of DU in subjects exposed to this pollutant. Once DU penetrates into the body via inhalation, ingestion, or skin contact, it gains the circulation and, thereby, spreads into every tissue/organ, particularly those rich in vessels such as the bone marrow. The longer the exposure and the greater the vascularization of a tissue/organ, the higher the probability of DU to accumulate and cause damage, through the stages depicted in Fig. 1.

potential generated through spontaneous inductive processes (genetic mutations) become overtly tumoral; 3. The determinant factors could be: a) the exposure time of the individual to DU; and b) the amount of vascularization of the tissue/organ. It is possible that for a very vascularized tissue/organ it is enough a reduced exposure time to favor the promotion and progression of a neoplasia but, for less vascularized tissues/organs a longer exposure time may be necessary to induce damage; and 4. One of the preferred sites for DU accumulation is the red bone marrow, a highly vascularized tissue. Exposure to DU has been correlated with a higher incidence of blood tumors, also in children [27–30]. However, this is not the only danger faced by a subject who, even after a reduced exposure time, undergoes an accumulation of DU in the bone marrow. In fact, DU can determine qualitative alterations of the hematopoietic process, including lowering of the innate anti-tumor immune response mediated by NK cells [14,15]. In turn, a reduced anti-tumor immune function can significantly increase the chances of tumor progression, including the formation of distant metastases.

Fig. 2 schematically shows the possible relationship between exposure to DU and the onset of tumors.

### Conclusions and perspectives for the future

The answer to the question “*Can depleted uranium cause cancer?*” is probably yes but, and this is a big but, it is extremely difficult to prove it directly in every case, like it happens for other pollutants. Nevertheless, the data demonstrating a close association between DU exposure and cancer development are abundant. Therefore, it would be unwise, even negligent, not to avoid exposure or not to monitor very carefully those that have been exposed for early diagnosis and immediate treatment if necessary. The problem is complicated because it is likely that DU can cause cancer mainly, or only, when other cofactors coincide with exposure to DU, such as genetic predispositions and/or alterations in the immune and/or chaperoning systems.

Nowadays the medical community is increasingly concerned about the risk of spending a period of several weeks or months in a militarized zone contaminated with DU nanoparticles because it may significantly increase the danger of cancer. What seems clear is that time spent in a contaminated area increases the risk of accumulating DU in various anatomical regions, including bone marrow.

Although the start (i.e., initiation step) of a tumor may be due to

chance and misfortune, evidence in the scientific literature implicates DU exposure in the occurrence of some cancers. DU may have a role in both the promotion and the progression of the tumor (Fig. 1), and also in the subsequent development of metastasis in various anatomical districts (e.g., lung, liver, brain, etc.) with fatal consequences. It is not possible to establish for the same patient with a tumor who has been exposed to DU whether, in the absence of DU exposure, the neoplasia would not have happened, or if it did happen whether it would have had the same aggressiveness and/or if the tumor progression would have been blocked by the immune system. However, there is enough evidence to encourage further investigation into the role of DU in carcinogenesis, directly and/or via modifications of one or more chaperones as a means to potentiate growth and dissemination. The fact that not all soldiers who serve in DU-contaminated war theaters develop cancer indicates that there has to be at least another causal factor converging in the same individual for DU to become carcinogenic: one candidate to investigate is alterations in, or collaboration of the chaperoning system.

In any case, a common sense recommendation would be to have all the necessary precautionary measures adopted (such as the use of protective suits and periodic air and water tests to check for the presence of DU) in the military operation theaters where DU ammunitions are or have been used, as well as health checks both before and after returning from the mission. If DU contamination is proven, subjects have to be treated, for instance, using chelating agents and/or other chemicals that are known to be effective in favoring elimination of DU and reducing the risk of toxicity [31].

Very importantly, health checks should not be limited to general screening (e.g., general medical examination and blood-cell counts) but should also include molecular tests to assess the status of the immune and chaperoning systems. Individuals in whom the innate immune defenses are low should be subjected to repeated and periodic screenings, taking advantage of the various modern diagnostic techniques (e.g., assessment of circulating DNA through liquid biopsy; detection of chaperone abnormalities). If alterations in one of more chaperones known to participate in carcinogenesis are detected, therapeutic measures targeting them should be implemented. These precautions would facilitate both primary (biological risk reduction) and secondary (early diagnosis) measures for the prevention of tumor pathologies potentially induced by DU.

Finally, in the immediate future, research on the microbiota and its role in DU toxicity and carcinogenesis should be encouraged and carried out. The interaction of the human microbiota with the immune and chaperoning systems has been determined to be of great potential interest in Medicine [32]. There has been increasing attention to the role of the gastrointestinal system microbes (microbiota) in the pathogenesis of cancer or immune regulation of cancer development or growth [33,34]. Furthermore, effects of depleted uranium on natural microbial systems have been reported [35], and the possibility of internal effects might be a subject for further examination. It is clear, then, that future efforts directed to prevent or combat the consequences of DU contamination should include research focused on the microbiota and its interactions with various tissues and systems in the human body.

### Conflict of interest

None.

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