International Journal of Medical and All Body Health Research

International Journal of Medical and all body Health Research
ISSN: 2582-8940
Received: 01-10-2020; Accepted: 17-10-2020
www.allmedicaljournal.com
Volume 1; Issue 4; October-December 2020; Page No. 27-31

Review on oppenheimer effect: The biomaterial-induced tissue sarcoma

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Abstract
When placing a solid material in a biological system, a biological reaction develops against it. This reaction varies in terms of intensity and time depending partially on material type. The term surface energy refers to the energy of the outer most atomic constitution of a material surface that can be estimated by calculating the critical surface tension of the surface. Theta surface refers to the outer most atomic constitution least retentive to glycoprotein which is measured through critical surface tension to be within the range of 20-30 mN/m. For applications require strong biological adhesion, the materials need to have higher surface energy than theta surface range. After implant, the material surface provokes a sequence of biological reactions eventually leading to biofilm development. Surprisingly, what is known as Oppenheimer effect shows an unexpected behavior of foreign body reaction to materials with different ranges of surface energy implanted in rats and mice. This unique behavior is still a big challenge to be explained. The yet unsolved phenomenon is the reason behind implanting a plastic sheet or film that induces sarcoma in rats while implanting the same material in the form of textile or powder induces almost no sarcoma. This review will focus on some various explanations based on historic and recent experimental work.

Keywords: Oppenheimer effect, Tissue sarcoma, Biomaterials, Foreign body reaction

Introduction
Cancer can be defined as the uncontrolled growth of body cells. Normally, body cells multiplied in response to body needs and then die when they are no longer needed. Cancer can develop and spread into all body organs and tissues through blood and lymph systems. Its etiology is still not conclusively proven. Genetic and environmental factors such as body tissue exposure to chemicals and radiation, viral diseases, and food related factors like alcohol and food poisoning play major roles in cancer development [1].

According to the National Cancer Institute (At the National Institutes of Health), it was reported that the most common cancer types in the United States, for example, are lung, bladder, breast, colon, kidney, endometrial, leukemia, melanoma, pancreas, prostate, and thyroid organs, estimating the annual cancer cases to more than 40,000 [2]. As each type of cancer is named according to the affected organ or tissue, cancer can be categorized into main categories; when it begins in the skin or the organ-lining or covering tissues, it is called carcinoma, while sarcoma refers to the connective and supportive tissue cancer like blood vessels, bone, cartilage, and muscles; when cancer affect blood forming tissue, like bone marrow, it is called leukemia (producing abnormal blood cells); when the cancer starts in the immune system, it is called lymphoma and myeloma [3].

Cancers, like any other diseases, have signs and symptoms. One sign or symptom is not enough to indicate cancer development; in fact, it could refer to other disease that affects the same organ or tissue. The most common sign and symptom related to cancer growth can be felt by pushing the surrounding organs and tissues including blood vessels and nerve producing pain and visible marks. Cancer can also be developed with no signs and symptoms or it may have specific signs that are not linked to the affected organ. This is possible since cancer cells sometimes release substances into the blood stream causing blood clotting in veins or they could increase calcium level in blood make the patient feel weak and dizzy [4]. Cancer development can be triggered or initiated by some implanted materials. Those materials surfaces and chemical properties can interfere with the normal biological processes of tissue cells.

Foreign Body Reaction
As the number of implantable medical devices and companies producing them is increasing, the more are the consequences and variety of tissue responses to these devices based on the foreign body reaction generalized through the tissue rejection process. According to Jones J. A. [5], "With all implanted medical devices a certain sequence of biological events occurs following implantation: injury, inflammatory cell infiltration, acute inflammation, chronic inflammation, granulation tissue formation, the foreign body reaction, and fibrosis."

These events can be varied in intensity according to the biomaterials chemical, physical, and surface properties and the particular organ tissue where the device is implanted. Foreign body reaction is known to be the end stage of wound healing responses that usually follow the medical device implantation involving macrophages and foreign body giant cells reaction, fusion, and adhesion to the adsorbed protein layer in response to the surface properties of the implanted material [6]. A major role in modulating the foreign body reaction during the first four weeks following medical device implantation is played by the biomaterial surface properties. It is important to understand this reaction as it may impact the medical device biocompatibility since some of the cases showed a reaction at tissue / material interface that lasted for the lifetime of the medical device [6]. The very early stage immediately after implantation, the first thing to happen is the adsorption of the glycoprotein as a result of dehydration. The glycoprotein adsorption initiates the blood material interactions which develop a blood-based transient provisional matrix on the biomaterial surface, this matrix develop the thrombus and blood clot formation [6]. The major characteristic that indicates the biocompatibility of the implanted device is the extent of the inflammatory reaction, which attempts either neutralizing or walling off the implanted device; acute inflammation which lasts from minutes to days is characterized by exudate formation and leukocytes infiltrating the area of the injury by migration, adhesion, emigration, and chemotaxis [5]. The chronic inflammation which can last from days to years, is characterized by neovascularization and the production of connective tissue at the site if injury, and there will be a decrease in the number of neutrophils and monocytes by differentiating into macrophages or undergoing cell death. Then, extra cellular matrix in the form of granulation tissue is produced by monocytes and macrophages at the healing stage [5].

Phagocytosis

An essential component of the innate immunity of the human body is the phagocyte system by which a various host defense functions were performed by specialized phagocytes (macrophages, monocytes and neutrophils) and rely on the phagocytic uptake of pathogens [7]. In order to distinguish the infectious agents and self, restricted phagocytic receptors have been evolved in macrophages even though the discrimination process is considered to be a primary challenge due to the large number of pathogens and their propensity to mutate [8]. Three important factors affect the phagocytes functions: the availability of sufficient phagocytes in the peripheral blood, their responsiveness to the signals from inflammatory sites, and their ability to migrate to these sites and kill the invaded microorganisms [9]. Along with the macrophages, there are neutrophils which comprise phagocytosis in a unique way throughout engulfing the pathogen and cell fragments to eliminate them [10]. A little knowledge exists about neutrophils due to the fact that most of the information about phagocytosis was derived from macrophages behavior.

Healthy Cell Behavior Vs. Cancer Cell Behavior

This In normal conditions, a healthy cell divides and grows based on special signals received from the neighbor cell and they stop dividing and growing when it receives signals indicated cell crowded environment, or its cellular machinery is defected, so it takes time to repair itself before proceeding with growing and division again [16]. When the cell is no longer able to repair itself or it underwent age, it will follow a process named as “apoptosis” which is kind of a programmed death process. Sometimes healthy cells continue to live but without function, and this is because the cell DNA is programmed to do certain number or divisions. Based on special signals sent by the cells, they get their oxygen and nutrients through blood which is regulated by vessels growth and distribution through a process called angiogenesis. In normal and healthy tissue, cells usually held in place attached to each other into a special structure that defines the function and properties of the specific tissue.

Compared to the healthy cells, cancer cells produce different and abnormal signals in terms of cell division and growth. They continue to divide to make new copies of the exact affected cell (damaged DNA cell) regardless of the situation of the surrounding cellular environment. Cancer cells continue producing signals for nutrition in a way that result in growing of new vessels among the tumor cells. When this vascularization occurs, the tissue will cross the line between being a precancerous and cancerous and becoming a true cancer. Through a process called metastasis, cancer cells can stop adhering to each other and relocating themselves. The process is one of the most defining characteristics of malignance which result in eruption of tumor in different parts on the body [16].

Most potentially developed cancer cells can be destroyed by many ways. Sometime the immune system detects the cancerous cell as a foreign body and attacks it. Another defense system can be triggered by young cancerous cell mutation which results in the cell destructing itself. Some cells can resist these kind of defenses and slipping away to produce a new, genetically-damaged, and uncontrolled generation of cells.

Oppenheimer Effect

About 50 years ago, some literature reported the development of sarcomas of subcutaneously implanted materials in rats. Those were the beginning of a wide range of experimental attempts that have been done to examine tumor induction as a result of foreign body reaction to implanted materials (metals and plastics). During that era it was found that the foreign body sarcoma was initiated around implanted materials regardless of their chemical inertness, and this is what is known later as solid-state carcinogenicity.

According to Oppenheimer 1956, several metals were tested on rats (silver, steel, tantalum, and vitallium), when samples in the form of circles and squares were (1.5cm) prepared and embedded subcutaneously in the abdominal wall of each rat. The highest incidence of tumor was induced by silver while sarcoma was induced in a lower incidence by vitallium, tantalum, and stainless steel. The types of tumor resulted were mainly fibro-sarcoma, with one case of osteogenic sarcoma [11].

On May 1957, the same team had conducted another experiment [12] for testing tumor induction by plastics in rats. They have tested several plastics types (cellophane, methyl methacrylate, nylon, Dacron, polyethylene, polystyrene, polyvinyl chloride, saran, silicone, and Vinyon) in 2 forms (sheet and powder). Each form of the same material was embedded subcutaneously on each side of the rat abdomen. Surprisingly, the film form had induced sarcoma while the powdered form did not. That raised the fact that the physical

form has everything to do with this phenomenon rather than the chemical properties. With a time series observation, the authors concluded that rare tumor was induced by the powdered form of plastics while high incidence of tumor accompanied with film form (55%). The embedded film was enclosed by a fibrous tissue sheath with a smooth inner wall that was isolated from the implanted film surface. Removing the film during the first 6 months of implant did not induce tumor as well as removing both the film and the pocket regardless of the time of removal showed no tumor development.

According to (Brand 1980), there is no correlation between the biomaterials and the specific histologic cell type in developing implant associated sarcoma, even though the tumor associated with the solid-state carcinogen is actually has mesenchymal origin [13]. He mentioned that from 98 foreign bodies or scare related cancer cases reported in the literature, over 25% were developed during the first 15 years, and about 50% developed during the first 25 years. After comparing these results to a substantial number of implants that were placed since the last 10-20 years, the incidence for tumor induction was lower. A prediction has been made based on this study that the incidence of tumor development at implantation sites would remain low [13].

Usually the tumor cells (sarcoma) adhere to the outer surface of the membranous sac that covers the implanted film rather than adhering to the film itself [14]. However, it was reported by Oppenheimer in 1955 that when tumor develops there will be no fibrous capsule surrounding the film implant which is mysterious since during the first few weeks after implants the fibrous capsule forms as a sheath enveloping the implant [15]. He also reported in the same publication that tumor cells form either adjacent or surrounding from one or both sides of the implant film (skin side or muscle side), and sometimes the film can even be projected from the tumor [15].

Oppenheimer and his team started a new set of experiments in an attempt to find an answer for the mysterious tumor induced by plastics. One of their explanations was since the polymer may include a intermolecular trapped monomers this might be the reason for tumor inducement, so they have tried several monomers like methyl methacrylate, 50% solution of styrene in benzene, 1% benzene solution of hexamethylene diamine (nylon component) by painting them on the back of rats and mice necks, but no tumor was induced only skin irritation. Another explanation was that maybe impurities like radicals and catalyst residue still existing in polymers could induce tumor, but in their experiment, the tumor was induced also by pure polymers like polyethylene [15].

When implanting polymers in textile form, there was no definite pocked formed around the implant, instead, the connective tissue was enmeshed by the material penetrating the threads and perforations of the textile form holding the implant in place with no sign of tumor formation or development [15]. The same thing when they implanted cotton fibers that are known as linters (the same material used for cellophane manufacturing) in rats, the fibers did not induce sarcoma while cellophane film implantation in mice in previous experiment resulted in tumor typically was fibrosarcoma [14].

Another interesting finding is when comparing the mechanical properties of the plastic film before implanting and after removal from the animal, most of the materials became more glossy and transparent while the alcohol extracted cellophane film loses some of its flexibility and becoming more dark by having some opaque patches with increased rigidity [14].

According to Baker 2007 [17], there are four possible explanations correlating the implant pore size with the incidence of sarcoma. The first one implies that the implant roughness, which is increases by increasing pore size, has something to do with the incidence of sarcoma. Other investigators disapproved this idea as they found that the slight increase in roughness (between 0.22 and 0.1µm) is difficult to indicate the transition between negative and positive tumorigencity. The second explanation is related to the surface area of the filter including inside the pores, but this cannot also explain the sudden change between negative and positive tumorogencity between filters with pore size o.22 and 0.1µm. The third possibility is about the effect of the surface charge correlated with the pore size on the incidence of sarcoma. Other investigators opposed this idea since both tumorgenic and nontumorogenic implants can be hydrophilic and electropositive, so they excluded this possibility. The fourth explanation is suggesting the effect of Millipore on disrupting cell communication. This does not fit the theory of stromal cells affecting epithelial cells because sarcomas are stromal cancers. However, small pore size could possibly affect stromal cells communication with each other. This was proven by a study conducted on mice by implanting Millipore filters with special pore sizes subcutaneously in each mouse. The results showed that the incidence of sarcoma was 11/11, 6/10, and 8/10 for pore sizes 0.025, 0.05, and 0.1µm, and no sarcoma was developed in the large pore group (0.45µ m) [18]. This experiment showed that the large group filters were attacked by macrophages and their cytoplasmic processes with extensive intercellular contact along the filter surface, while the small pore size group showed no reaction between macrophages and the filters, only fibrous tissue capsules formed quickly creating a prominent demarcation between cells and implant surface [18].

A later experiment was made by Iomhair and Lavelle (1997) [19] to compare the surface area of the implanted filter and the incidence of sarcoma development around the filters in 40 mice. All filters Millipore size was about 0.45µm. the independent variables in this study were single layer, paired, and trios as the surface area was increasing by layers. Surprisingly the results showed that no tumor was induced in the single layers group while 7 cases developed tumor in the paired group, and 16 cases of tumor in the trios group. The conclusion was based on these results is that the surface area of the implant could give us the answer why sarcoma was induced in rats and not observed often in human as the average implant is relatively larger in rats and mice than in human.

Another study made earlier by Brand et al. [20] on female mice by implanting un-plasticized vinyl chloride and vinyl acetate copolymer in the form of single and multiple films. The results showed that tumor induction was provoked and sped up as the number of film layers was increased and the size of the single film was increased too. One year before that study the same team did an experiment by implanting 0.2-mm films of the same copolymer. 6 months after implantation, the films and the tissue capsule around it were removed and transplanted in recipient animals, and after 3 months, part of the capsule and the cell layers over it was derived and cultured separately. The cultured cells, which were implanted in hybrid recipients at different passage numbers, gave rise to homologous type tumors. So, they made the conclusion that

specific tumor determined cells preparation is possible to be prepared in vitro [21]. 8 years before that work, they had conducted an experiment on mice in an attempt to compare premalignant cells maturation after transplant [22]. The study was basically involving cutting the plastic inserts and tissue capsules in half within monthly intervals. One half remained in the animal and the other half was transplanted into another recipient. After examination, the tumors in the original and the recipient were identical in terms of chromosome stemlines and premalignant maturation. What they found is that there was no cell division occurred in the film-attached cells (premalignant cells) as they were in a dormant state for months before tumor appearance. Later on, these cells detach from the film and invade the capsule tissue to propagate and produce the tumor within 4 weeks [22].

A recent study was made to compare the foreign body reaction against biodegradable polymers between rats and mice [23]. hexamethylenediisocyanate crosslinked dermal sheep collagen disks were implanted subcutaneously in rats and mice. The disks were explanted after 7, 14, 21, and 28 days and evaluated by light and transmission electron microscope. The results showed that in mice, there was less giant cell formation as well as phagocytosis against the implanted disk, which was rarely occurred in mice or it was much slower than in rats. However, the stromal tissue was more abundant in mice than in rats. Therefore, these differences can greatly affect the experimental outcomes in this aspect if they were not taken into account.

In 1977, a study was made by Brinton-Darnell M. and Brand I. [25] showed a delayed foreign body tumor development in mice. This study consists of implanting unplasticized vinyl chloride-vinyl acetate copolymer films on 2 groups of mice (the control and lactate dehydrogenase virus infected group). The tumorogenesis was delayed in the virus-infected male and female mice for 2 months. However, the researchers did not agree on the effect of LDV effect on the cellular immunity as the foreign body tumorogenesis is not affected by cellular immunity. Another study was done on mice by Michelich VJ, Brand KG. (1980) [26], to determine the effect of gonadectomy on foreign body reaction on mice. The results showed no significant effect. However, there was a significant effect of estrogen influencing the pace of foreign body tumor induction in mice.

Conclusion

Some factors were suggested to explain the Oppenheimer effect related to the physical form of the implant also including to the pore size and surface area. Material type is not a much of an effective factor for developing sarcoma in mice and rats. The animal's general physiology differs greatly when it is compared to human. Considering the biological reaction against implants, which is usually faster if not more aggressive in these animals (mice and rats), the results may not be applicable to humans. The most reasonable explanation for foreign body induced sarcoma is that both rats and mice biological response and the implant continuous surface area disrupting cell communication on both sides of the implanted film tend to develop tumor-like behavior in cells trying to accommodate the implant. Since there are very few cases of sarcoma development against textile or porous forms (filter forms) than the film form implants of the same materials, the shape of the implant almost has everything to do with tumor development. Disruption and interference with cell communication in addition to the fast rate of biological response of these animals could be a plausible interpretation for Oppenheimer effect.

References

1. Cancer ADAM. Medical Encyclopedia. PubMed Health. Available from: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002267/ (accessed 10/23/2012)
2. National Cancer Institute. Common Cancer Types. National Institutes of Health. Available from: http://www.cancer.gov/cancertopics/types/commoncancers (accessed 10/23/2012)
3. National Cancer Institute. What is cancer? National institutes of Health. Available from: http://www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer (accessed 10/27/2012)
4. American cancer society. Signs and Symptoms of Cancer. Available from: http://www.cancer.org/cancer/cancerbasics/signs-and-symptoms-of-cancer (accessed 10/27/2012)
5. Jones J. A. Biomaterials and the foreign body reaction: Surface chemistry dependent macrophage adhesion, fusion, apoptosis, and cytokine production. 2007. Doctoral dissertation. Biomedical engineering.
6. Anderson JM, Rodriguez A, Chang DT. Foreign body reaction to biomaterials. Seminars in immunology. 2008; 20:86-100.
7. Filias A, Theodorou GL, Mouzopoulou M, Varvarigou AA, Mantagos S, Karakantza M. Phagocytic ability of neutrophils and monocytes in neonates. BMC Pediatrics. 2011; 11(29):1-6.
8. Aderem A, Underhill DM, Mechanisms of phagocytosis in macrophages. Annu. Rev. Immunol. 1999; 17:593-623.
9. Pinna S. amyloid protein-a cause of diabetes. Available from: http://drpinna.com/amyloid-protein-a-cause-of-diabetes-9103 (accessed 10/28/2012)
10. Lee WL, Harrison RE, Grinstein S. Phagocytosis by neutrophils. Microbes and infection / Institut Pasteur. 2003; 5:1299-306.
11. Oppenheimer BS, Oppenheimer ET, Danishefsky I, Stout AP. Carcinogenic effect of metals in rodents. Cancer Res. 1956;16(5):439-441.
12. Oppenheimer BS, Oppenheimer ET, Stout AP, Willhite M, Danishefsky I. The latent period in carcinogenesis by plastics in rats and its relation to the presarcomatous stage. Cancer. 1958;11(1):204-13.
13. Brand GK, Brand I. Risk assessment of carcinogenesis at implantation sites. Plastic and Reconstruction Surgery. 1980; 66:591-594.
14. Oppenheimer BS, Oppenheimer ET, Stout AP. Sarcomas induced by imbedding various plastic films. Proceedings of the Society for Experimental Biology and Medicine. 1952; 79(3):366-369.
15. Oppenheimer BS, Oppenheimer ET, Danishefsky I, Stout AP, Eirich F. Further studies of polymers as carcinogenic agents in animals. Cancer Research 1955; 15:333-340.
16. Cancer. Cell behaving badly. Microscope Imaging Station. Avilable from: http://www.exploratorium.edu/imaging_station/research/cancer/story_cancer.pdf (accessed: 11/8/2012).
17. Baker SG, Kramer BS. Paradoxes in carcinogenesis: new opportunities for research directions. BMC Cancer.

2007; 7:151.
18. Karp RD, Johnson KH, Buoen LC, Ghobrial HK, Brand I, Brand KG. Tumorigenesis by Millipore filters in mice: histology and ultrastructure of tissue reactions as related to pore size. J Natl Cancer Inst. 1973;51(4):1275-85.
19. Iomhair MM, Lavelle SM. Effect of film size on production of foreign body sarcoma by perforated film implants. Technol Health Care. 1997; 5(4):331-4.
20. Brand KG, Buoen LC, Brand I. Multiphasic incidence of foreign body-induced sarcomas. Cancer Res. 1976; 36(10):3681-3.
21. Buoen LC, Brand I, Brand KG. Foreign-body tumorigenesis: in vitro isolation and expansion of preneoplastic clonal cell populations. J Natl Cancer Inst. 1975; 55(3):721-3.
22. Brand KG, Buoen LC, Brand I. Carcinogenesis from polymer implants: new aspects from chromosomal and transplantation studies during premalignancy. J Natl Cancer Inst. 1967; 39(4):663-79.
23. Khouw IM, van Wachem PB, Molema G, Plantinga JA, de Leij LF, van Luyn MJ. The foreign body reaction to a biodegradable biomaterial differs between rats and mice. J Biomed Mater Res. 2000; 52(3):439-46.
24. Baier RE. Surface behavior of biomaterials: The theta surface for biocompatibility. Journal of Material Science: Materials in Medicine. 2006; 17:1057-62.
25. Brinton-Darnell M, Brand I. Delayed foreign-body tumorigenesis in mice infected with lactate dehydrogenase-elevating virus: Brief communication. J Natl Cancer Inst. 1977; 59(3):1027-9.
26. Michelich VJ, Brand KG. Effects of gonadectomy on foreign-body tumorigenesis in CBA/H mice. J Natl Cancer Inst. 1980; 64(4):807-8.