Apoptosis, Angiogenesis and Radiation Treatment

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INTRODUCTION

Modern approach in treating cancer cases is a combination of various modality treatment, operation, radiation and drugs with tumor cell target. To obtain accurate prediction factor of cancer treatment response such as chemo or radiotherapy, many studies have been conducted recently on various biology parameter such as expression of various oncogenes, tumor suppressor gene, apoptosis controlling gene, cell cycle, angiogenesis, etc, else than various clinical parameter that has been used today.

Likewise in treatment, else than conventional treatment, today the treatment that using various molecular mechanisms, which can effect tumor cell survival as its target has been developed. That mechanism including inhibition of growth factor receptor (GFR), angiogenesis, signal transduction pathway (STP), and apoptosis, proliferation, etc.

The programmed cell death, known as apoptosis is an activation process of genetic program, which is resulted by developmental or environmental stimulus, which causes cell death and destruction. Since 1982, apoptosis process has been related to radiation induced cell death (RICD), then various study about it have been developed continuously, and in 1986-1989, it has been reported that this process has important role in RICD of post mitotic cells. Start since 1990, studies about this process has been conducted on various animal and human tumors model, and also on various cell lines. Even though the cell death that resulted from radiation is not only caused by apoptosis, but also spontaneous apoptosis and apoptosis after radiation therapy may have important role in vivo.

Nowadays a very significant understanding about process or mechanism has been started; it is about cellular and molecular mechanism of how is the formation of new blood vessel from the existed blood vessel of healthy people and in certain disease, which are known as angiogenesis. There are 2 kind of abnormality in this process, insufficiency and excessive-ness, such as in malignancy process. Thus the treatment principle of this antiangiogenic is to recover this process on its normal speed mechanism.

Solid tumor consists of various components, such as normal cell and stroma, extra cell matrix and blood vessel. Cell life very depended on continuous oxygen and nutrient supply, that being carried by blood, so that every cell in the body must have adequate distance from capillary. Tissues will not grow with diameter over 1 mm without the formation of new blood vessel. Likewise in tumor cell, thus it seems that new blood vessel formation is a must in tumor metastases and growth. Then nowadays, angiogenesis is regarded as one of the most important thing in affecting malignancy growth and metastasis.

There are various cytotoxic therapies such as chemo and radiotherapy, which in fact will increase this angiogenesis response, and that is one of causes of therapy failure. Thus antiangiogenic combination as part of cancer therapy together with other modality is rational.

This paper will discuss about recent literature about correlation of apoptosis, angiogenesis process and its relationship to the response of radiation therapy.

PHYSICAL AND BIOLOGICAL BASIC OF RADIATION THERAPY

Radiotherapy or radiation therapy is a treatment using ionizing ray. Since X-ray has been found by Wilhelm Conrad Roentgen in 1895 and he used that ray in treatment, there is so many advances in basic science (cellular radiobiology, molecular or radio physics), clinical application of that ray, and radiation utility and
equipment advance in keeping with technology progress.

Ionizing Ray is an electromagnetic ray (photon) or energized particle that causes ionization process if it passes various materials including biologic material. Ionization process is electron transfer from neighboring orbit of atomic nucleus or molecule that passed by ionizing ray, thus the atom or molecule will have over positive loading, which is known as ion. Depend on the stage and target of damage that occurred, this ionization process could cause cell death. Direct effect will occur if the exposed target is important component of intra cell, i.e. DNA, which is the control center of intracellular activity. The indirect effect resulted from free radicals formation, caused by ionization process on water molecule, which is 70% of cell. These free radicals have a very destructive nature, which after pass various chemical chain processes then, finally it could cause cell death.

Various kind of DNA damage that occur on the processes mentioned above, is followed by induction of expression p53, which will inhibit cell cycle, which has that DNA defect in G1 phase. The repairing process, which is induced by p53, will be occurred, either completely or not. In certain damage condition, if there is no repairing process anymore, then the cell will be programmed to experience death which known as apoptosis (figure 1).

Biological factors that effect cell response to radiation; 1). Oxygenation. Oxygen is a very patent chemical modification of radiation sensitivity, with potency effect of 2.5 - 3 times, 2). Proliferation phases. Theory, which explains that cell in phase G2, and M is a radiosensitive cell group such as related to main target of cell death, i.e. DNA. In those phases there is greatest number of DNA. Other theory also says that there is maximal cell repair capability in phase G1 and S. 3). Thermal. Besides it has cytotoxic effect, thermal also can be used as potenciator of the radiation effect.

APOPTOSIS

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Figure 1. p53 Induce The Process of The DNA Damaged Apoptosis and Cell Death

The term of apoptosis firstly introduced by Kerr et. all 1972 as the process of cell death which occur inn tissue normal development (embryonic & tissue homeostasis) and organ normal development (organogenesis), and after some of toxic therapy, such as radiation. This is differed from other cell death, which is known as necrosis process. Apoptosis term is taken from Greek language, which means the falling leaves of tree as physiologic process that happens naturally.

Apoptosis vs Necrosis

The cell death particularly caused by apoptosis else than necrosis. Characteristic of necrosis cell is loss of membrane integrity before DNA degradation, whereas the characteristic of apoptosis is loss of membrane integrity after DNA degradation. DNA degradation in apoptosis appears as DNA fragment in 1180-200 base pairs (bp) length, in keeping with hypothesis that this is caused by endonuclease that will cut DNA on internucleosomal location.

Apoptosis begin by pre-condensation phase i.e. stimulus of specific tissue, which cause transcription process, alteration, and activation of certain gene set. This process is followed by condensation of nucleus
chromatin in periphery of nucleus, followed by *blebbing* of nucleus and cytoplasm membrane. This process will be continued by fragmentation of DNA and the remaining nucleus structure which will develop into discrete membrane that wrapping the apoptotic bodies.\(^5,6,8\) There is no inflammatory response in apoptosis process.

In some system, apoptosis occurs on cell before entering the fission (interphase apoptosis = IA), whereas in other system apoptosis can occur on cells that has finished its cell cycle which is ended by mitosis, either with or without chromosomal aberration (mitotic apoptosis with chromosomal aberration = MCA, without chromosomal aberration = MA).\(^5\)

Necrosis is a cell death process that is not part of normal development, but it is a response of trauma or damage of chemical and toxic material. This condition is differed morphologically or biochemical characteristic and uncontrolled genetically.\(^5,6,8\) Morphological change which begin from swollen cell and followed by membrane rupture and it can be stimulus for inflammatory process of neighboring tissue. DNA degradation after necrosis process occurs randomly without any certain measure range.\(^5,6,8\)

In vivo, apoptosis appears as individual cell that frequently phagocytized by the neighboring cell or macrophage. While necrosis cell appears as unity of cell groups plus inflammatory reaction nearby because of releasing of necrotizing cell contain.\(^5\)

### Apoptosis in Normal and Pathologic Tissue

The tissue and organ growth are increment of size, cell amount or both, which experienced by a group of cell that actively proliferate. Adult human is growth outcome because of increment of cell amount (proliferation) of one cell that has been fertilized, and also because of increment of cell size. After adolescence, then the cell amount remains constant and there is no growth anymore, even in this state mitosis as a part of proliferation process is still occur in order to substitute the death cell, particularly that caused by apoptosis process, else than necrosis resulted from various etiology factor. This balance condition must be controlled. When the death cell amount is larger than the increment cell amount, then it will be shrinkage or diminution of tissue or organ size, as occurs holistically in the elderly.

Today apoptosis is regarded as a process that has very important role in various physiologic condition.\(^22\) such as bcl2 which has function in maintaining viability of lymphocyte, melanocyte, intestine and kidney epithelial, in developmental phase.\(^3\) Dysregulation of this process will cause various defect start from malignancy to AIDS.\(^23\) Even though in various malignancy there are very various apoptosis levels.\(^24\)

Inadequacy of p-53 function and bcl-2, both are important controlling factor of apoptosis. They have direct correlation with cancer case.\(^3\) Even though this condition is caused by interference of apoptosis process, it also can be caused by shortening of proliferation duration or activation of the entering cell from not proliferating actively into actively proliferated.

Apoptosis is also part of pathologic process, which caused by viral infection, such as adenovirus, baculovirus or HIV and influenza virus. The obstacles of apoptosis process are much related to persistency or latency of those virus.\(^5\) In cervix malignancy, HPV presence seems related to apoptosis process interference, which also affect differentiation of tumor cell.\(^25\) In the study using cell line of Burkitt lymphoma, it reveals that the presence of EBV-LMP1 will inhibit p53-triggered apoptosis.\(^25\) In Nasopharyngeal Carcinoma the presence of EBV-LMP1 will inhibit the apoptosis process in vivo and this has significant correlation to the tumor growth and lymph node involvement.\(^26\)

### Various Controlling Genes of Apoptosis

As controlling genes, either it is controlling factor of positive growth or various controlling factor of negative growth, it could be as controlling mechanism of cell existence or cell death process, and the balance, it is needed in developmental process.\(^4\)

Environmental process may also affect apoptosis, and DNA damage is a very obvious example.\(^4\) The cell which experiences permanent DNA damage and can not be repaired, will be deleted by apoptosis process. The function of protein p53 (TSP = tumor suppressor protein) is to react against DNA damage, which is caused by various things, i.e. radiation and it may start the apoptosis induction process.\(^4,27\)

The other stimulus processes that may occur and will increase the p53 existence are viral infection, dysfunction of positive growth controlling, cell damage, and also loss contact between cell and cell or cell and substrate.\(^4\) (Figure 2)

In the case of colon, head and neck and cervix malignancy, there are strong correlation between apoptosis process and WT p53 existence in *in vitro* study. Then gene therapy is implemented by using that tumor suppressor gene.\(^28-30\) In colon malignancy, the apoptosis index has strong correlation with proliferation level and it affects the tumor growth.\(^31\)

Cell existence or cell death can be directly controlled
by signal transduction pathway (STP) controlling or indirectly by regulation of transcription process. Where various transcription process regulator will also regulate apoptosis i.e. c-myc, p53, E2F, c-fos, etc.  

Hence, it could be concluded that apoptosis controlling mechanism is involving so many genes, which globally divided into 3 groups : genes which suppress the apoptosis process such as interleukin-1b converting enzyme (ICE) and intermediate genes such as Fas / fas ligand, p53, myc, WAF1.

Figure 3 reveals apoptosis controlling mechanism, which is very complicated.

Figure 2. p53 in Apoptosis and Its Relation to The Other Gene

Radiation Induced Apoptosis (RIA)

Uckun" demonstrates that in human B-lymphocyte, first step of RIA is by tyrosine phosphorylation, which will develop into clonogene cell death.

This RIA firstly observed in cryptic cell of small intestine, 3-6 hours post radiation of 0.5 – 10 Gy, that 2 % apoptosis (IA) occur. Even though this amount is not fascinating but it is observed and actually this event occur in cell which is actively proliferated such as in the brain cell, kidney, intestine, testis, etc.  

In the human tumor cells, apoptosis may be also observed particularly in hemopoietic tissue, lymphoid and other tissue such as ovaries, colon and also cervix, either as spontaneous apoptosis or after post radiation apoptosis.  

Some act actually may modify the post radiation apoptosis, which reveals tendency that membrane is also a target, which could induce apoptosis. This is visible in lidocaine protection to salivary gland against radiation effect.  

Nevertheless the apoptosis upgrading by BuRD or 125I distribution, which bind to DNA chain reveals that DNA is an important target in apoptosis induction.  

We assume that in the IA induction through membrane target has important role, while in MCA or MA induction through DNA target is more important.  

ANGIOGENESIS

The understanding of this important process has been recently begun. It is a mechanism about how does new blood vessel formed by cellular or molecular in healthy person and in certain disease. Abnormality of angiogenesis process may occur in 2 types that are insufficiency of that process or excessive angiogenesis process, such as occur in various disease condition, one of it is solid tumor. Therapy approach is based on this process, it is also depend on the condition, and it could be stimulus or inhibition of this angiogenesis process.  

Controlling Mechanism in Angiogenesis Process

Vasculogenesis and angiogenesis process are 2 important things and it is 2 physiologic processes that quite different where vasculogenesis is development of circulation system at first development of embryo, while normal angiogenesis is new blood vessel formation from capillary blood vessel, which has been formed at the end of embryo and post natal development.  

Angiogenesis is very depending on the proliferation regulation and tube formation by capillary endothelial cell, which physiologically these cell is in quiescent condition and it will perform mitosis in a very slow period. But in activated condition of angiogenesis process, those cells will be out of quiescent condition and it will divide fast, as fast as the bone marrow cells. This pathological condition may occur in various diseases such as arthritis, skin disease, and in neoplasm this condition it hardly ceased spontaneously. Hence in malignancy disease, the basic treatment of antiangiogenesis is to return the micro vessel proliferation into its normal condition and prevent the regeneration.  

There are some modulators of angiogenesis process as follow:

1. Estrogen  
2. Nitric oxide  
3. Reactive oxygen  
4. Hemodynamic forces  
5. Oxygen in angiogenesis tumor  
6. Fibrin and proteolysis in reparation process  
7. E-selectin in angiogenesis tumor and metastases
Angiogenesis and Tumor Growth

The cell existence is very dependent on continuous oxygen and nutrient supply, which is carried by blood, so that each cell in the body must have adequate distance from capillary blood vessel. Tissue will not grow in diameter more than 1 mm before forming new blood vessel. Likewise in tumor cell, so it appears that the new blood formation is a must condition in the tumor growth and metastases.²

There are 2 mechanisms, which cause angiogenic switch in tumor vascularization, i.e.:³

1. Stochastic mutation at genetic level either by downregulation of inhibition control (negative control) or upregulation of stimulation control (positive control) of angiogenesis process, which is known as genetic angiogenic switch.

2. Ischemia-induced angiogenesis, which in normal condition, the ischemic tissue will detect lack of oxygen or glucose and responding through induction, which results the angiogenesis production factor. Tumor cells also have that ability.

From the animal study, it seems that the second mechanism is more dominant in tumor neovascularization process.

Alteration of that angiogenesis activity is a very complicated condition. It is a balance condition between controlling mechanism against stimulus (positive control) and inhibition (negative control). In this condition, negative control will be downregulated. There are 14 factors of positive control of that process, which mostly studies are basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). Those components are found in most tumors. Upregulation of those factors usually accompanied by downregulation of inhibition factor such as thrombospondin, which is produced under control of wild p53. As has been known that in carcinogenesis process, there is frequent event of this wild P53 mutation, so that negative controlling mechanism of angiogenesis is also disrupted. It is also found that various tumor suppressor genes are negative control against angiogenesis process.⁴

Ischemia-induced angiogenesis stages in tumor angiogenesis are as follow:⁵

1. Sensor of oxygen level by the tumor cell
2. Ischemia will regulate the tumor angiogenesis
3. Blood vessel maturation

Ischemia stress gives important contribution to tumor angiogenesis as physiologic angiogenesis. Glucose and oxygen level will be recognized by tumor cell, and this information will activate the HIF1 transcription factor. HIF1 will control various gene target that regulate energy balance either by regulating nutrient supply for the need of tumor cell or balancing the tumor.
metabolism against the exist nutrient. Hence there will be balance between progression and regression of blood vessel. Main effector for HIF1 is VEGF which is angiogenic factor an also survival factor for the new blood vessel. Studies of various animals reveal that HIF1-VEGF complex which is controlled by oxygen / glucose level is a very important factor in tumor angiogenesis regulation. The complicated correlation of HIF1-VEGF by genetic angiogenic switch hypothesis is activation of that complex through certain oncogene pathway, that affected by microenvironmental stress.

Alteration of angiogenesis activation from quiescent condition may occur on multistage process of carcinogenesis mechanism. This angiogenesis may occur either before the multistage process has begun (i.e. cervix cancer), or after the process has begun (i.e. in breast cancer, etc). In those things above, the tumor development from in situ condition may occur by those angiogenesis process.34

After neovascularization surround the in situ tumor has occurred, the tumor cell will be affected by survival and growth factors, not only because of increasing perfusion effect but also because of paracrine effect. Perfusion effect will temporarily increase the nutrient and oxygen when tumor cell population could be achieve, while the paracrine effect of tumor neovascularization which is resulted by growth factor and cytokine, which is resulted by endothelial, will continuously stimulate the growth and migration of tumor cell. Endothelial cell produce various growth factor and cytokine, such as interleukine 6-8. In many studies, interleukine 6 will stimulate motility of breast cancer cell so that it will increase probability of tumor cell entering the circulation.34

This paracrine effect may also stimulate tumor growth by other mechanism. Where there are 2 compartment of tumor growth. First compartment is endothelial cell and the other compartment is tumor cell. Both of them may stimulate each growth, but if the endothelial cell does not get any stimulus because there is inhibition material, then the tumor group will also be inhibited.34

The existence of this two compartment will become basic cytotoxic administration including radiation together with anti-angiogenesis. Where tumor cell group will be mutated so that resulting resistance to cytotoxic agent, then that will not happen to the endothelial cell group, hence as end result, there will be a response against combination of those two-modality therapy.1,3,4

**APOPTOSIS AND ANGIOGENESIS ROLE IN RADIATION THERAPY**

In order to get accurate prediction factor of cancer therapy response, various studies in various biology parameter such as expression of various oncogene, tumor suppressor gene, apoptosis controlling gene, cell cycle, angiogenesis, etc, in correlation to radiation therapy and also chemotherapy, nowadays has been conducted, else than using various clinical parameter that recently has been widely used.

Likewise in treatment, else than the conventional therapy, nowadays there is development of treatment, which has target as molecular mechanism, which will affect tumor cells. Including in that mechanism are GFR inhibition, angiogenesis, STP, apoptosis modulation, etc.3

Apoptosis relevance and the result of radiation therapy

Even though the cell death because of radiation is not only caused by apoptosis, but spontaneous apoptosis and apoptosis post radiation may have very important role in vivo.3 In salivary gland, acute reaction because of radiation is caused by apoptosis process, likewise in experimental animal, it appears that TCD (Tumor cure dose) 50 and TGD (Tumor Growth Delay) have strong correlation to spontaneous apoptosis and RIA. From that figure, we see that SGD is lengthen after administration of equal amount of dose by increasing the spontaneous apoptosis index and post radiation index. Likewise, it appears that TCD 50 will increase by lowering the spontaneous and post radiation apoptosis index. Although it is very vary on various kind of tumor.5

The mutated P53 is frequently related to resistance condition either against chemo or radiotherapy.35 Moreover in animal study, it is proven that p53 is needed in RIA process.36 The other researcher reveals correlation between apoptosis index with 5 ysr and local reoccurrence. There is significant correlation between 5 ysr (79% vs. 47%) and local reoccurrence (79% vs.61%) between tumor with lower apoptosis index and upper apoptosis index.

Abe demonstrates that group of tumor with higher spontaneous apoptosis index will give better result of chemo-radiation therapy.17 In non-small cell lungs carcinoma, it appears that the p53 expression and apoptosis index are prediction factor of therapy success.38

In my study about naso-pharyngeal carcinoma (Dana Risbin IPTEKDOM V), it reveals about very significant correlation between tumor spontaneous apoptosis index before therapy and the tumor response result against
radiation. In the tumor with low apoptosis index then the tumor response against radiation is significantly decreased. 

**Antiangiogenetic Relevance and Radiation Response**

Modern approach in malignancy management is combination of therapy modality, operation, radiation and chemotherapy and drugs that have target on tumor cell. 

Solid tumor consists of various component i.e. normal cell and stroma, extra cellular matrix, and blood vessel. To grow and metastases tumor must stimulate new blood vessel formation through angiogenesis process. Up to now tumor’s blood vessel is also important target in malignancy therapy. 

Teknos also in his study using patient with laryngeal malignancy demonstrates that MV (micro vessel density) is one of angiogenesis parameter that can be used as prediction factor of good response against radiation or chemotherapy. said that angiogenesis can be used as prediction factor of response against cytotoxic therapy either chemotherapy or radiation. Where tumor with bad oxygenation is known as resistant group against radiation or chemotherapy. 

Koukourakis also suggested doing tumor classification based on its angiogenesis capability, and this can be use as tumor cell identification group, which has advantage of radiation therapy only, combination with chemotherapy or with antiangiogenesis.

The radiotherapy and chemotherapy administration in Koukourakis study demonstrates increasing of angiogenesis process, which will increase proliferation and inhibit apoptosis. This is related to radiation therapy failure in the SCC patient of head and neck. It will cause tumor re-growth. Ning also demonstrates the same thing in his study using animal, where there is VEGF, FGF and also PDGF increase, which are important regulator in induction of angiogenesis process.

In animal experiment, Jain demonstrates that administration of anti VEGF (as one important mediator in angiogenesis induction) can regress the blood vessel, and permeability of blood vessel, so that oxygen level will increase. So, the anti VEGF administration together with modality either chemo or radiotherapy will increase the therapy response. 

Herbst demonstrates in his study by administration of rh-Endo for cancer patient as antiangiogenic may increase apoptosis on tumor cell and endothelial.

Ning demonstrates rise of tumor cell death because of radiation after antiangiogenic administration (SU5416, or SU 6668) receptor inhibitor VEGF, FGF and also PDGF. Gorski also demonstrates that anti VEGF administration could increase the effect of anti-tumor on in vitro study. 

The IMC-C225 administration as anti EGFR which competitively will bind the EGF receptor seems good on in vitro study, and on clinical study phase 1 in head and neck malignancy patient together with chemo and radiotherapy. It appears could inhibit proliferation, angiogenesis, and metastases and also increases apoptosis. Hence, it could increase the therapy response. Clinical study has also been done by ECOG by using combination of IMC-C225 with various cytotoxic therapy.

This is also demonstrated by Huang by giving ZD 1839 (Iressa) as EGFR inhibitor orally together with radiation in animal, and it could inhibit proliferation, angiogenesis and also increase the radiation induced apoptosis. This is also demonstrated by Schmidt.

Dicker found that radiation administration together with Cox 2 inhibitor will inhibit proliferation, migration, and differentiation of endothelial cell significantly twice. And also this Cox 2 inhibitor has been proven on in vitro and animal study that it has anti-angiogenic effect and increases apoptosis. And its study as tumor growth inhibitor on colo-rectal malignancy is being conducted recently. Up to now, we begin to introduce it use together with chemo or radiotherapy.

**CONCLUSION**

Apoptosis is complicated mechanism and involving many things either oncogene role or tumor suppressor genes, which has important role in normal process and its dys-regulation is found in various kind of disease.

Morphologically and by its existence process, we could differ necrosis as the cause of the other cell death, RICD particularly caused by apoptosis else than necrosis.

Angiogenesis is a formation process of new blood vessel, and recently it is regarded as important factor for induction of tumor growth and metastases by 2 type of different mechanism.

Radiation or chemotherapy administration increase angiogenesis and this is related to the therapy failure.

There are 2 compartment in tumor period i.e. tumor cell and endothelial compartment, where both of it mutually affected, and this become basic rational in administering combination therapy of antiangiogenic drug with modality of cytotoxic therapy such as radiation and chemotherapy.

Recently, in vitro and animal experimental study have been develop and even clinical study has been also
begun about these two biological mechanism usage either as prediction factor of therapy response or as combination with other modality of cytotoxic therapy in order to increase the therapy result.

Spontaneous apoptosis and angiogenesis can be used as prediction factor of radiation therapy response. Malignancy with high spontaneous apoptosis factor will give better radiation therapy result.

Angiogenesis is also can be used as prediction factor of therapy response, malignancy with high angiogenesis level is indicator against worse therapy result in the future and it will reveal low RICD.

There are very rational basic in giving therapy combination of this anti angiogenesis and other modality therapy particularly radiation.

REFERENCES
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