Editorial

Physical and Chemical Agents Inducing Cell Death and Differentiation

Cell death and differentiation represent different types of cell response to environmental stimuli. The focus of the present issue is to outline physical and chemical conditions responsible for inducing various modes of cell damage and death useful for successful anti-cancer treatment. In recent years new demanding fields of research have developed with the aim of studying human exposure to environmental chemical, physical or biological agents to increase the knowledge of the mechanisms and dynamics of events causing adverse health effects [1]. This topic deserves particular attention in light of the impact that climate changes, global warming and pollution are having on human health and habitat.

When compared to the chemical induction of apoptosis, relatively little is known about cell treatment with physical agents. According to epidemiological findings and compelling experimental evidences, ultraviolet radiation (UVR) appears to be the most important environmental carcinogen, whose harmful effects can be prevented through education and accurate photo-protective strategies at skin and ocular level [2]. UV, ionizing radiation (IR), reactive oxygen species (ROS) and a number of chemicals, including anti-neoplastic drugs, induce DNA damage, which can be repaired by the co-ordinated action of the DNA repair system and cell cycle checkpoint controls or, if not, can result in cell cytotoxicity or senescence [2-7]. Though direct as well as indirect, non-targeted and delayed effects (bystander and adaptive responses, genomic instability) of radiation or chemical exposure need to be further evaluated in terms of cancer risk assessment [8], it is evident that cell detrimental effects induced by both physical and chemical agents have been greatly exploited in cancer therapy. Interestingly, in light of its capability of inducing apoptosis, hyperthermia has become the fifth strategy, after surgery, chemotherapy, radiation and biological therapy, in the fight against cancer [9]. Moreover, during the last decades, a better understanding of cancer biology has led to the development of new promising therapeutic approaches, based on "molecular targeted" drugs, directed against specific "target" molecules playing a key role in tumour maintenance [10]. Among these molecules, protein kinases (e.g. tyrosine kinase, serine/threonine kinase) play a key role in tumorigenesis, cancer progression and metastasis and, thus, represent ideal anti-cancer therapeutic targets [11]. Small kinase inhibitors or monoclonal antibodies have been used as monotherapy or in combination with conventional treatments (chemotherapy or radiotherapy) to reduce the common emergence of drug or radiation resistance. In this respect, the design of PI3K or multi-target inhibitors appears to be a promising tool for the treatment of tumours even after development of resistance to traditional chemotherapy [12].

Besides oncogenes over-expression and cell cycle control mechanisms disruption, mutations in apoptotic regulators (namely p53) are very frequent in cancer cells and represent for them a way to escape toxic effects inducible with chemo/radiotherapy. As an alternative strategy to restoring transcriptional activation to mutant p53 proteins in solid tumours, small molecule selective inhibitors of p53/MDM2 interaction (Nutlins) are emerging as an innovative tool in the treatment of malignancies expressing wild-type p53 including haematological disorders [5].

Based on these findings, the topic of this issue was chosen to improve our understanding of therapeutic potential of physical and chemical anti-cancer strategies.

In the opening paper "Signalling Pathways Activated by Ultraviolet Radiation: Role in Ocular and Cutaneous Health" [2], Dr. N. Di Girolamo provides clinical and experimental findings highlighting the importance of ultraviolet radiation (UVR) as the key trigger for ocular and cutaneous disorders. An overview of the effects of different UV wavelengths (UVA, UVB, UVC) on the eye and skin is reported with a particular emphasis on a UV-induced ocular disease known as pterygium. The article provides a valuable insight into the processes and signal transduction pathways activated by UVR at cellular level and mediating both cell death (apoptosis) and survival (autophagy) responses, indicating the molecular basis of chemopreventive potential of retinoids in UVR-associated epidermal and ocular damage.

The second review "Morpho-Functional Features of *In-Vitro* Cell Death Induced by Physical Agents" by Dr. S. Burattini and co-authors [9] summarizes the present knowledge on the apoptogenic effect of some physical agents (hypo- or hyperthermia, UVR, mild static magnetic fields) on several cell types, mostly in culture systems. The authors outline the usefulness of hyperthermia in the treatment of advanced cancer and demonstrate with nice pictures, obtained with transmission and scanning electron microscopy as well as with TUNEL technique, the morphological features of different types of cell damage and death induced by the different agents.

The third review "Cell Responses to Oxidative Stressors" by Prof. A. Cataldi [6] takes into consideration stimuli acting as potential stressors for cell homeostasis among which ionizing radiation, hypoxia, hyperoxia and chemotherapeutics. The article focuses the attention to the role played by mitochondria in the physiological and non-physiological signalling responses of eukaryotic cells to oxidative stressors and gives evidence to detrimental but also beneficial effects of ROS, up to recent years considered harmful but currently assigned a role as mediators of physiological processes, like cell differentiation, proliferation and migration.

The next three reviews deal with new avenues in cancer treatment based on "molecular targeted" drugs.

Dr. V. Cepero *et al.* with the article "Tyrosine Kinases as Molecular Targets to Inhibit Cancer Progression and Metastasis" [11] make an extensive overview of the most clinically advanced anti-cancer targeted therapies directed against both tyrosine and serin-threonin kinases. The paper underlines also the concept of oncogene addiction and the importance of combination therapies to fight against resistance emergence. The review "PI3K/Akt Signalling Pathway Specific Inhibitors: a Novel Strategy to Sensitize Cancer Cells to Anti-Cancer Drugs" by Prof. M. Falasca [12] is focused on the role of PI3K/Akt pathway in cancer development and progression and, moreover, in induction of chemotherapy resistance. In particular, the author reports on novel therapeutic agents inhibiting different components of the PI3K/Akt pathway and discusses results of preclinical studies and first clinical trials highlighting promises and requirements of this therapeutic approach. In the review "Cell Cycle as a Target of Antineoplastic Drugs" [7] Dr. M. De Falco and Prof. A. De Luca summarize key regulatory events of cell cycle progression and unscheduled neoplastic proliferation. Drawing from this background, the authors provide a wide and up-to-date description of critical cell cycle regulators specific inhibitors used as novel anticancer drugs in several preclinical and clinical trials with particular regard to cyclin-dependent kinases (cdk), Polo mitotic kinases and Aurora kinases inhibitors.

The last paper in this issue "Nutlins and ionizing radiation in cancer therapy" by Dr. G. Impicciatore *et al.* [5] complements the previous reviews providing to the readers a deepen insight into molecular mechanisms of ionizing radiation sensitivity or resistance of neoplastic cells and designing the rationale for a combined approach employing physical (IR) and chemical (Nutlins) agents to increase outcome in cancer therapy.

Finally, I would like to thank all the authors for their excellent contributions as well as the Editorial Board and all the referees for their generous and competent help in the editing process. I do hope that this hot topic issue will be of interest to a broad audience and useful to the scientific community to draw new strategic approaches in cancer treatment.

REFERENCES

[1] Gomez-Mejiba SE, Zhai Z, Akram H, Pye QN, Hensley K, Kurien BT, *et al.* Inhalation of environmental stressors & chronic inflammation: autoimmunity and neurodegeneration. Mutat Res 2009; 674(1-2): 62-72.
[2] Di Girolamo N. Signalling pathways activated by ultraviolet radiation: role in ocular and cutaneous health. Curr Pharm Des 2010; 16(12): 1358-75.
[3] Su TT. Cellular responses to DNA damage: one signal, multiple choices. Annu Rev Genet 2006; 40: 187-08.
[4] Hornsby PJ. Senescence as anticancer mechanism. J Clin Oncol 2007; 28: 177-86.
[5] Impicciatore G, Sancilio S, Miscia S, Di Pietro R. Nutlins and ionizing radiation in cancer therapy. Curr Pharm Des 2010; 16(12): 1427-42.
[6] Cataldi A. Cell responses to oxidative stressors. Curr Pharm Des 2010; 16(12): 1387-95.
[7] De Falco M, De Luca A. Cell cycle as a target of antineoplastic drugs. Curr Pharm Des 2010; 16(12): 1417-26.
[8] Preston RJ. Bystander effects, genomic instability, adaptive response, and cancer risk assessment for radiation and chemical exposures. Toxicol Appl Pharm 2005; 207 (2): S550-56.
[9] Burattini S, Battistelli M, Falcieri E. Morpho-functional features of *in vitro* cell death induced by physical agents. Curr Pharm Des 2010; 16(12): 1376-86.
[10] Urruticoechea A, Alemany R, Balart J, Villanueva A, Vinals F, Capella G. Recent advances in cancer therapy: an overview. Curr Pharm Des 2010; 16(1): 3-10.
[11] Cepero V, Sierra JR, Giordano S. Tyrosine kinases as molecular targets to inhibit cancer progression and metastasis. Curr Pharm Des 2010; 16(12): 1396-409.
[12] Falasca M. PI3K/Akt signalling pathway specific inhibitors: a novel strategy to sensitize cancer cells to anti-cancer drugs. Curr Pharm Des 2010; 16(12): 1410-16.

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