Recent Developments in Anti-Cancer Drug Research

According to the World Health Organization, cancer is the second leading cause of death in the World and it is thought to have caused around 9.6 million deaths in 2018 [1]. Despite many recent advances in diagnosis and therapy, the incidence of cancer continues to rise, and exponentially, and it is thought that by 2025 more than 20 million new cases will have been identified [2]. Hence it is no surprise to find that there is much research being done on diseases known collectively as cancer, and that a very large body of literature is continuously becoming available on the subject. Reviewing this information periodically will bring together the most important aspects, and make them directly available to those interested. Having this in mind, this special issue was planned. It contains seven reviews on recent developments in the field.

Marques and coworkers discuss the possibilities of using hexokinase isoform 2 (HK2), one of the five HK isoforms involved in the regulation of glycolysis, known to be overexpressed in many types of cancer and consequently of having enhanced activity, as a drug target for cancer therapy [3]. The hexokinases seem to be logical targets, since an increase in glycolysis is a characteristic of cancer cells, which use glucose as their main fuel. This nutrient is critical for their proliferation and survival. HK2 plays a significant role in insulin-sensitive tissues, but it is structurally very similar to HK1, the most relevant HK isoform in terms of general effects and distribution in the body. Experiments have shown that deletion of HK2 reduces cancer cell proliferation by one half, without any explicit side effects in adult mice, which suggests that HK2 could be a therapeutic target.

In their review, after a brief overview on central metabolism, and on glycolysis in particular, Marques and coworkers look at the function, expression and activity of HKs, their structures and known inhibitors [3]. They report on the known effects of HK2 ablation/inhibition, and compare the structures and sequences of HK1 and HK2 isoforms, so as to unveil differences that can be explored in the design of selective inhibitors for therapeutic purposes. For example, it is known that some properties of HK1 and HK2 are different, such as their sensitivity to inhibition by G6P or their response to the presence of Pi. In addition, despite being structurally very similar, only HK2 has shown catalytic activity in both the N- and C-terminus domains, unlike HK1 and HK3, in which the N-terminal domain is exclusively dedicated to a regulatory function. This discussion is followed by a review of the main HK1/2 inhibitors known and by a summary of the other biological roles played by HK1 and HK2.

Another recognized target for cancer therapy is mutant p53. P53 is a gene present in multicellular organisms, which plays a critical role in preventing cancer formation. It becomes activated in response to a variety of stress stimuli, e.g. DNA damage, oncogene activation, hypoxia or nutrient deprivation. Once activated, p53 functions as a sequence–specific transcription factor, initiating a series of reactions which cause DNA repair or cell-cycle arrest and apoptosis, in response to these stresses. P53 is inactivated in most cancers, either by overexpression of its inhibitors or by mutations. The development of drugs which can restore the p53 function is an active area of research, since this is recognized as a possible strategy to treat cancer. In their review, Santos and coworkers describe the most relevant mutant p53 small molecule reactivators developed so far, their characteristics and effects on cancer [4]. Despite much promise, so far no small molecule reactivators have entered clinical trials, which suggests that further development work is needed, particularly to improve selectivity and lower adverse side effects.

The reviews by Chiacchio and coworkers [5], Pilli and coworkers [6], and by Andrade and Martins [7], look at specific classes of molecules, of interest in anticancer drug development. Chiacchio and coworkers focus oxazoles, five-membered ring heterocyclic compounds containing nitrogen and oxygen atoms in their core structure, as well as their dehydrogenated derivatives, iso/oxazolines and iso/oxazolidines [5]. These substances are known to display important anticancer activities, some in the nanomolar range. In fact, in 2015 about 30% of FDA-approved anticancer drugs had one or more rings containing nitrogen or oxygen. In their review, the authors summarize the literature published in the last ten years on oxazole-based compounds displaying anticancer activity, highlighting synthetic routes and the relevant anticancer properties.
Pilli and coworkers focused on goniothalamin and related styryl lactones, secondary metabolites which occur in all the plants of the genus Goniothalamus. Goniothalamin itself was isolated from the bark of Cryptocarya caloneura (Laureaceae), which is used in folk medicine [6]. These lactones are characterized by a C6-C3-C4 carbon backbone bearing a pyran-2-one motif and include in their structure a linked styryl or modified styryl fragment. Most of the substances isolated so far display (R)-configuration at C-6, which has inspired the development of several synthetic routes based on asymmetric synthesis. Many display antimicrobial or anticancer activity. Yet, their cytotoxic effects seem to be specific to cancer cells, which makes them promising candidates for drug development, although a biological target remains to be defined. The authors review the literature pertaining to styryl lactones isolated for the first time from 2000-2017, focusing on their syntheses, biological activity and mechanisms of action.

Metal complexes have been used in medicinal chemistry for long, and in fact cis-diaminedichloro-platinum(II), also known as cisplatin, which was approved for anticancer therapy 40 years ago, still remains one of the most widely used anticancer drugs. It is very efficient in some cases. Another two platinum-based anticancer drugs have been approved worldwide for the treatment of a variety of cancers: carboplatin, and oxaliplatin. However, the development of resistance to these drugs, or unwanted side effects, make further research in this area a necessity. Some scorpionate-based metal complexes have been found to have useful anticancer properties. Andrade and Martins review the literature on this subject [7]. Hence potassium, cobalt, copper, ruthenium, silver, the lanthanides and other group III metal ions have been used to make stable complexes with scorpionate ligands, which show useful cytotoxic effects on cancer cells. Scorpionate metal complexes which release carbon monoxide have also been developed. In this case the metal complex functions as a prodrug, for the controlled delivery of carbon monoxide to cells. Examples of scorpionate metal complexes which act as photosensitizers were also included. However, despite all the interesting results obtained so far, the research on the topic of cytotoxic scorpionate metal complexes is still very much underdeveloped. The studies reported refer to in vitro determinations with one exception, a ruthenium(II)-arene complex, designated UNICAM-1, which was slightly more active than NAMI I, when tested in a model of triple negative breast cancer, a cancer type with the worst negative outcome and prognosis, which displays aggressive metastatic behaviour and for which there are yet not many therapeutic options. NAMI I is a ruthenium complex which is under development for the treatment of some forms of cancer, and has already passed phase II trials.

Faisca Phillips and Pombeiro concentrated on transition metal-based prodrugs for anticancer drug delivery [8]. Ideally prodrugs, once administered, travel unchanged throughout the body until the tumor site, where a cytotoxic component is released into its active form and destroys cancer cells. In this way it causes minimal damage to the surrounding tissues and toxic side effects are minimized. Transforming metal complexes into prodrugs may also improve biological properties so that they can be taken-up orally, it may improve redox stability, cancer targeting and cellular uptake. The prodrug can also be made so that it carries additional drugs to the required site, so as to increase overall drug potency and efficacy. The existing transition metal-based prodrugs are triggered to release the cytotoxic agent in many ways: by differences in oxygen concentration or in pH, by the action of overexpressed enzymes, by differences in metabolic rates, etc., which distinguish cancer cells from normal ones, or even by the input of radiation, which can be visible light. Due to the large body of information available on this subject, this review is focused on prodrugs of complexes of cobalt, ruthenium and platinum only. Several substances are presently being tested, some platinum prodrugs have even reached clinical trials, however none has yet been approved for medical use. The development of experimental techniques which allow drug release to be followed in real time, e.g. the use of fluorescent ligands and imaging techniques, is expected to accelerate developments in this field.

The use of ionic liquids (ILs) in topical drug delivery is reviewed by Gomes, Ferraz and coworkers [9]. Topical delivery implies that a site of action located within the skin structure itself is targeted, rather than a transdermal application, in which the drug reaches the blood stream and causes systemic effects. Due to their ionic nature, ILs can increase the solubility and permeability of a drug, and consequently its bioavailability. They have become important agents for drug development. The use of ionic liquids in topical drug delivery holds great promise for the treatment of skin cancers, and the latest generation of ionic liquids may also display an anti-proliferative action, a topic which is also covered in this review. Ionic liquid-based vesicles, micelles, and microemulsions have been explored, and the results obtained so far are promising. The studies reported on the transport of specific drugs are revised too.
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REFERENCES


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