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Mini-review

Screening and identification of molecular targets for cancer therapy

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ABSTRACT

In recent decades, targeted therapeutics have significantly improved therapy results in patients with malignant tumors of different origins. However, malignant diseases characterized by aggressiveness and increased capacity for metastatic spread still require basic researchers and clinicians to direct enormous efforts toward the development of novel therapeutic targets. Potential targets should be selected with the clinical endpoint in view; targeted therapeutics can be developed: for use in combination with currently existing therapeutic approaches in order to improve their efficacy; to overcome the treatment resistance of tumor cells and thus protect the patient from recurrence; to repress molecular mechanisms related to immune escape of cancer cells; and to combat the metastatic dissemination of carcinoma cells. Taking into account the specific clinical aim that should be achieved, different strategies and techniques can be proposed to identify the most promising candidate molecules for further development as therapeutic targets. Since cellular membranes contain a large number of druggable molecules, evaluation of the membrane protein profiles of carcinoma cells having different properties can provide a basis for further development of therapeutic targets. This review considers how cellular membranes obtained from different pre-clinical and clinical samples can be used in screening and to identify targets for cancer therapy.

Introduction

In 2015, in the European Union (28 countries) and worldwide, respectively, there will be a predicted 2.8 and 15.2 million new cases of cancer, and 1.3 and 8.2 million cancer-related deaths (http://globocan.iarc.fr). Clinicians and basic researchers continue their efforts to improve clinical outcome in cancer patients: novel anti-tumor compounds and surgical and radiotherapy techniques are continually being developed. However, the problem of tumor relapse after treatment remains unsolved [1–3]. It is generally believed that both local and distant recurrences develop from treatment-resistant carcinoma cells which survive treatment with anti-tumor therapies. This stimulates interest in the discovery of novel agents targeting treatment-resistant carcinoma cells and helping to overcome chemo- and radioresistance. Logically, targeted compounds or chemotherapeutics can damage and eliminate treatment-resistant carcinoma cells effectively by inhibiting the molecular pathways that contribute to cancer cell chemo- and radioresistance and to their increased survival capacity. Hence, identifying these pathways in malignant tumors will provide the basis for developing targeted therapeutics capable of destroying the most aggressive carcinoma cells. Additionally, assessing the intratumoral presence of carcinoma cells potentially resistant to conventional treatment approaches will contribute to the emergence of personalized therapy schedules. Newly developed chemotherapeutics can be used either alone to destroy aggressive and treatment-resistant cells or in combination with currently existing standard therapeutic approaches to improve their efficacy and to overcome primary and/or secondary therapy resistance. However, it is generally believed that elucidation of molecular mechanisms underlying unfavorable disease outcome can help fight malignant diseases better. Despite the relatively short period of time in which researchers worked on this problem, a variety of signaling molecules and pathways were shown to be implicated as causes of treatment failure. Thus, recent findings have shown that a number of intratumoral and intracellular events can be associated with decreased tumor response to anti-tumor therapy: tumor hypoxia, DNA damage response pathway, affected cell death regulation, compromised cell cycle regulation, activated efflux pumps and signal transduction pathways, etc. [4–8].

The era of personalized medicine in oncology began more than two decades ago, when the first molecules characterizing tumor

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aggressiveness were identified and used for diagnostic and therapeutic applications. ErbB family members (ErbB1 or epidermal growth factor receptor (EGFR); ErbB2 or Her2/neu) are the most studied and prominent molecules contributing to cancer cell aggressiveness, disease progression and therapy resistance in breast, lung, head and neck and colorectal cancer patients [9–11]. ErbB family members were used to develop targeting antibodies and small molecules in order to inhibit ErbB-dependent pathways in carcinoma cells. It is now known that administration of blockers of ErbB-related intracellular pathways (anti-EGFR antibodies and small molecules; anti-Her2/neu antibodies) markedly improved disease-free and overall survival rates in head and neck, colorectal, lung and breast cancer patients [12–14].

Despite the results so far achieved, clinicians have still failed to improve survival rate markedly in cancer patients with metastatic disease, and death rates from metastatic cancers have remained mostly unchanged over the past three decades [15]. For these reasons, the molecular perturbations that underlie aggressive behavior in carcinoma cells and endue them with abilities for metastatic spread should be investigated to enable discovery of novel biomarkers and therapeutic targets which can then be targeted to reduce the risk of local and distant recurrence after administration of currently existing therapeutic approaches.

What is an ideal therapeutic target?

Modern technologies in molecular cancer biology provide the basis for the discovery of promising therapeutic targets. Ever more molecules are being investigated which may become candidates for the development of novel targeted compounds. Unfortunately, not all these molecules meet the requirements to be considered as ideal therapeutic targets. Thus, a molecule can be proposed for further development as a drug target if it is present in a majority of patients having a specific tumor type and if it has a strong relationship to carcinogenesis. Any potential target molecule should therefore be analyzed for its role in carcinoma cell formation and in acquisition of cancer-related molecular properties such as resistance to apoptosis, uncontrolled cell proliferation, increased cell migration, altered cellular adhesiveness, and overcoming the immune response. A molecule may already be of potential interest if it shows a strong link with at least one cancer hallmark.

Ideally, a target candidate should not be expressed in normal noncancerous tissues [16]. The reasons underlying this statement are, firstly, that only malignant tissues should be targeted by the drug and, secondly, therapeutic approaches should not give rise to severe side effects and toxicities in normal tissues. Thus, in order to avoid the occurrence of adverse events in cancer patients upon treatment, the candidate target molecule should be evaluated comprehensively for its involvement in the physiology of a range of different organs and systems. Unfortunately, this is a big challenge to find a target candidate that will be expressed only in malignant cells. The majority of the molecules considered as potential therapeutic targets demonstrate only overexpression in malignant tissues compared to non-malignant tissues.

Next, the potential therapeutic target should be capable of assay, to facilitate both the screening of patients and the monitoring of response to treatment or of disease progression. Increased expression or activity of the molecule of interest can serve as a signal to define a group of patients who will be treated with the targeted therapeutics. Both the expression and the activity of a target candidate can be important for drug development. Targeted therapeutics can bind to an overexpressed molecule, thus modulating the intracellular signals originating with that molecule, and therefore inhibiting cell proliferation or even causing cell death. Thus, target-specific antibodies bind to the target molecule and block target-associated signaling, whereas small molecules can impair an activated target-specific pathway chemically without repressing expression of the target on the cancer cells [17,18]. In order to develop a highly specific and effective targeting compound, it is necessary to select druggable target molecules. Unfortunately, not all target candidates are druggable. Thus, Owens in her report indicated that only one-tenth of the human genome codes for druggable molecules, and only half of these are relevant to disease [19].

Cellular membrane as a source of druggable targets

As mentioned above, a target candidate can be druggable if its expression and/or activity can be affected or modulated by small molecular weight compounds or by candidate-specific antibodies. Extracellular proteins and membrane receptors are valuable sources for development of therapeutic targets, due to their critical roles in maintaining cellular homeostasis between intracellular cytosol and extracellular microenvironment [20,21]. Membrane-associated proteins represent more than two-thirds of the therapeutic targets for drugs that are presently marketed or that are being developed [20,22]. Membrane proteins can be divided into three subgroups, depending on their localization and crosstalk with lipid bilayers, namely, integral, anchored or peripheral [20,23]. Membrane-associated molecules with extracellular domains have the following advantages over intracellular proteins: first of all, they can be easily detected on the cancer cell surface; secondly, agents targeted to them do not need to enter the cancer cell in order to reach an intracellular target molecule; thirdly, surface proteins are molecules of interest for the development of drug- or radionuclide-conjugated targeted compounds for use in imaging technologies; and fourthly, membrane-associated receptors can be used for development of target-specific antibodies and small molecules which block the extracellular domain or inhibit the activity of intracellular domain(s). Additionally, membrane receptors and proteins are responsible for initiating and transmitting signals required for the maintenance of cells' functional activities [24]. This fact also supports the idea of blocking expression and/or activity of membrane proteins in order to inhibit cancer cell functions related to cell survival, proliferation, differentiation and metastatic spread.

Targeted agents can be used to reach different endpoints in cancer prevention and treatment. They can be administered (1) to prevent cancer formation; (2) to treat primary tumors; (3) to improve tumor response to chemo- and radiotherapy and to overcome primary or acquired chemo-radioresistance in carcinoma cells and thus protect patients from recurrence; and (4) to protect patients from or to combat the metastatic spread of malignant tumors. Of course, among agents that are effective in the treatment of malignant diseases at specific stages of tumor progression or in enhancing conventional therapeutic approaches, targeted compounds which allow all the endpoints to be achieved are the best choice. On the other hand, it is likely that clinicians would observe markedly higher efficacy in targeted compounds created for specific purposes, e.g. to eliminate the most aggressive carcinoma cells possessing treatment resistance, or cells with metastatic properties. In order to design highly effective targeted compounds selectively destroying such carcinoma cells, it will be necessary to identify molecules and pathways indispensable for these cells. For this, evaluating the membrane protein profiles in carcinoma cells with specific properties can help to identify surface proteins and receptors involved in cell formation and activity. As shown in Fig. 1, breast carcinoma cells with different migratory capacities exhibit different membrane properties. Thus, migratory MDA-MB-231 cells have a higher ability to attach to a glass surface than do parental cells characterized by markedly lower migration and invasive capabilities. Furthermore, migratory cells characteristically have a larger cell surface and enhanced formation of exosomes. As recently reported, an increased cell membrane area may be associated with malignant behaviors