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Review

Approaches for targeting mitochondria in cancer therapy☆

Gerard G.M. D'Souza *, Mayura A Wagle, Vaibhav Saxena, Anee Shah

Department of Pharmaceutical Sciences, Massachusetts College of Pharmacy and Health Sciences, Boston, MA, USA

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ABSTRACT

The recognition of the role that mitochondria play in human health and disease is evidenced by the emergence in recent decades of a whole new field of "Mitochondrial Medicine". Molecules located on or inside mitochondria are considered prime pharmacological targets and a wide range of efforts are underway to exploit these targets to develop targeted therapies for various diseases including cancer. However the concept of targeting, while seemingly simple in theory, has multiple subtly different practical approaches. The focus of this article is to highlight these differences in the context of a discussion on the current status of various mitochondria-targeted approaches to cancer therapy. This article is part of a Special Issue entitled: Bioenergetics of Cancer.

1. The concept of targeting: appropriate use of "target" and "targeting"

Currently the terms target and targeting are used so commonly that to question their meaning might seem strange. However, for the purpose of this review we wish to first offer our thoughts on the concept of targeting and appropriate use and context of the terms targeting and target. To begin with, it must be appreciated that drug therapy at the most fundamental level is the interaction of two molecules. An exogenous molecule administered to a patient and the molecule in the patient that the administered molecule interacts with to initiate a physiological response. In an ideal scenario, the administered molecule interacts with only one physiological molecule and produces a physiological response that improves a patient's condition. In this context it is clear that the term target may be applied to the physiological molecule and the administered molecule is a drug. The concept of targeting on the other hand has multiple definitions and can often be the source of confusion if not communicated clearly.

From a drug discovery perspective, targeting is very often described in terms of the drug molecule's ability to interact only with the target. This concept is best described by the use of the term selectivity and is very different from the concept of targeting from a military perspective where the term arguably first originated. Consider a bullet fired from a gun as an example. The object the bullet is intended to hit is the target, and the act of aiming the gun so the bullet hits the target is what constitutes targeting. The action that the bullet produces is destruction of the target. This action is indiscriminate in that if the bullet hits an object other than the target, that object will be destroyed as well. Using the gunshot analogy to illustrate the drug discovery perspective on targeting would involve firing bullets that only destroy the target but leave the non-targets unharmed. Most approaches to disease therapy have followed such an argument: finding such selective molecules has been relatively easy when there were significant differences between the disease causing process and normal human biochemical pathways. Not surprisingly, infectious diseases are relatively easier to treat than inherent disorders. The selectivity is however dose dependent and most drugs that are considered to be selectively toxic to invading pathogens are in fact toxic to human cells as well, but at higher doses.

The current challenges in drug therapy lie in the treatment of diseases associated with malfunctions of normal human biochemical pathways in certain tissues. More often than not, even dose dependent selectivity is hard to achieve. Therefore the concept of targeting is becoming more and more associated with selective delivery. The term 'targeting' should ideally imply that the molecule is in some way able to selectively accumulate at an intended site of action and that the selective accumulation is associated with its selective action. This distinction is particularly important in developing targeted therapy for a disease like cancer. Unless unique molecular targets found exclusively (or at sufficiently higher levels) in the diseased state and not in normal state are discovered, selective accumulation at the disease site is crucial to the improvement of therapy. In summary, it can be said that there appear to be two distinct approaches to targeting in the context of drug therapy. The

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* Corresponding author. 179 Longwood Avenue, Boston, MA, 02115, USA.
E-mail address: gerard.dsouza@mcphs.edu (G.G.M. D'Souza).

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first involves selective action on the target while the second involves selective accumulation at the target. Most if not all examples of targeting seem to end up being the combination of some degree of selective action on the target and some degree of selective accumulation at the site of the target. Improving the degree of selective accumulation has the added advantage, even for molecules with high target selective action, of reducing the required dose and hence should be a major focus of all targeting approaches.

In the context of drug molecules the properties of selective accumulation are associated with the concept of bioavailability and biodistribution that are related to the physico-chemical properties of the molecule. To overcome the limitations that a compound's physico-chemical properties can impose on its potential pharmaceutical application, the process of large-scale screening of chemical libraries has been extended beyond identifying desired bioactivity. Screening approaches routinely incorporate selection for physico-chemical properties that are known to confer high bioavailability as well. Unfortunately, this approach often leads to many potent molecules being excluded from further development. These molecules often have a potent pharmacological action at a desired molecular target but aren't able to find their way exclusively to that target. It is almost certain that there is a growing list of such molecules that are in essence potential drugs if only a delivery strategy can be devised to get them to their molecular target in the human body.

Fig. 1 is a schematic representation of the levels of targeting that might be necessary in the treatment of cancer by a targeting approach. After systemic administration, the drug has to reach the tumor mass that is composed of tumor cells and the supporting stroma. The stroma, in turn, is made up of connective tissue, blood vessels, and other non-malignant cells. Therefore, drug accumulation in a solid tumor is only the first step in selective action against cancer. The drug still has to reach the tumor cell, and once inside the cell, it has to reach its final sub-cellular target. The sub-cellular target might be a cytosolic molecule or more often than not, might be a molecule that is on or inside a membrane bound organelle. In the latter case the drug must also be able to enter the organelle and then find its molecular target. Currently, drug targeting is well accepted till the cellular level as evidenced by the large number of approaches being explored to achieve cell-specific accumulation of drugs. However, targeting at a sub-cellular level has until recently not been as widely pursued perhaps due to technological limitations or the argument that once a drug gets inside a cell it will eventually find its way to the sub-cellular target. In the context of cancer therapy mitochondria are widely recognized to be the location of several potential drug targets.

2. Mitochondrial targets for cancer therapy

The mitochondrion is an important organelle that mediates several critical processes in a eukaryotic cell. Of prime importance in the physiology of cancer is the role of mitochondria in energy metabolism and regulation of cell cycle. There is strong evidence to support the rationale for the development of anticancer strategies based on mitochondrial targets. Mitochondria are known to play a key role in the complex apoptotic mechanism and trigger cell death via several mechanisms that include disrupting electron transport and energy metabolism, releasing or activating proteins that mediate apoptosis and altering cellular redox potential. [1–3]. A critical event leading to programmed cell death is the mitochondrial membrane permeabilization, which is under the control of the permeability transition pore complex (mPTPC), a multiprotein complex formed at the contact site between the mitochondrial inner and outer membranes. Apoptosis plays a central role in tissue homeostasis and it is generally recognized that inhibition of apoptosis contributes to the transformation process of normal cells into cancer cells [4]. The dysfunction of most apoptosis regulating pathways has been found to be linked to various types of cancer [5,6]. The key role of mitochondrial dysfunction and altered apoptotic regulatory mechanisms has been appreciated for more than a decade [7–10]. Closely allied with the dysregulation of mitochondrial involvement in the apoptotic process is the altered role of mitochondria in the energy metabolism of malignant cells [11]. Cancer cells are known to favor the glycolytic process as a source of ATP, even under aerobic conditions. Such adaptations are believed to contribute to invasive and adaptive advantages and are often the result of changes in mitochondrial function including mutations in mitochondrial DNA (mtDNA) [12]. Therefore this organelle is increasingly described as a “prime target” for pharmacological intervention [13] and there is a growing interest in the study of the molecular interactions of xenobiotics with cellular components located on or inside the mitochondrion. Research by several groups has identified various mitochondria associated molecular targets for bioactive molecules [14–18]. These targets include mtDNA, the mitochondrial respiratory chain, the mitochondrial permeability transition pore complex (mPTPC), potassium channels on the mitochondria and the various mitochondria associated anti and pro-apoptotic factors to name a few [13,14,19]. An exhaustive discussion of the various mechanistic pathways and all potential target molecules in mitochondria of cancer cells has been the subject of several excellent reviews published over the past few years [11,20–22] and as such will not be the major focus of this article. More relevant to the intent of this article is the discussion of current examples of so-called mitochondrial targeting and how they fit into the concept of targeting as discussed in the previous section. With this in mind, two major approaches can be envisioned for targeting mitochondria in cancer cells. The first involves the use of molecules that act exclusively on molecular targets in mitochondria of cancer cells without having any marked predisposition for preferentially accumulating in mitochondria. The second approach involves delivering molecules capable of affecting mitochondrial function exclusively to the mitochondria of cancer cells. Of course as discussed earlier the two approaches need not be exclusive with the best

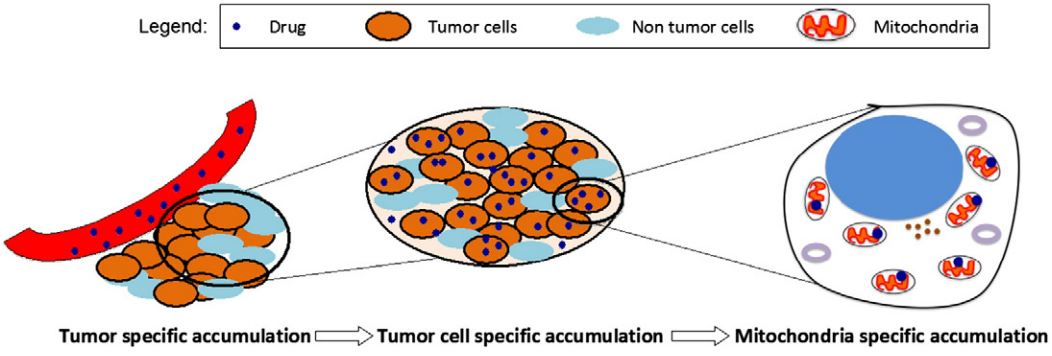

Fig. 1. A schematic representation of the levels of selective accumulation required in a mitochondria-specific targeting strategy.