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Redefining the Limits of Biochemistry in Multidrug Resistant Nematodes: Implications for Future Drug Development

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MDR and Nematode Parasites

Chemotherapy remains the foremost available tool for the control of nematode parasites. However, the substantial use of anthelmintics, combined with a scarcity of new anthelmintic classes, has led to a gradual increase in the resistance of nematode parasites to these compounds. Multi-Drug Resistance (MDR) in economically important livestock nematodes, such as *Haemonchus contortus* enables the parasite to effectively 'escape' the effects of existing anthelmintics and represents a major obstacle to sustainable livestock farming and food production [1]. The growth in anthelmintic resistance has led to an increasing need for novel chemotherapeutic compounds.

Despite this unmet need, there has been a decline in anthelmintic research and development due to contraction of the industry, economic factors and regulatory requirements, among others [2]. Recently, two new anthelmintics have been released; however, resistant parasites are anticipated to appear in about a decade after the lunching of products, regardless their chemical structure or their mode of action. Hence, understanding the mechanisms of Drug Resistance (DR) in parasites is crucial for medical, veterinary, economic and eco-toxicological reasons and for maintaining the effectiveness of current anthelmintic drugs.

Among the different tactics by which nematode parasites tolerate the action of anthelmintic, those affecting influx and efflux are of special significance, as they limit the interaction of the chemical compound with its intracellular targets and hence, its lethal effects on the parasite. Mechanisms of drug evasion based on the intracellular extrusion of the drug and/or modification of target molecules have been described [3,4]. Cellular mechanisms related to metabolic activity have also been seen in eukaryotic systems, e.g. cancer cells. Recent observations suggest that such mechanism may occur in nematodes [5].

Drug Transporter Mediating MDR: Beyond the Obvious

Albeit an important body of works, fundamental questions remain unsolved that may, once understood allow us to design new therapeutic strategies. A structural study has enabled the molecular basis of P-gp (the archetypal drug transporter in cancer cells) to be defined with remarkable precision [6]. This study confirms that when ATP molecules bind to Pgp, conformational changes promote a "power stroke", leading to the passage of drugs from the membrane inner leaflet into the outer milieu [6,7]. Although the molecular model of Pgp has permitted a relatively simple representation of MDR in agreement with the usual concepts from the field of biochemistry, how a single protein can expel structurally different drugs, is still poorly understood. How P-gp recognizes hundreds of different hydrophobic drugs and pump them out of the cell is still debatable [8]. Nonetheless, there is something far more important at stake: the Pgp-like-mediated MDR model does not conform to the fundamental notion of specificity and seems to challenge the roots of biochemistry. This conceptual issue was noted very early in this field, and raised clearly by Paul Roepe [9]: "...MDR cells are resistant to, and/or exhibit decreased retention of literally hundreds of different hydrophobic compounds that are structurally divergent. Membrane transporters, like soluble enzymes, are exquisitely substrate-specific. If transporters were not specific, the cell would eventually become a high entropy chaotic mess, as there are no structural molecular motifs common to all the many different agents to which MDR cells are resistant. MDR protein is a very unusual enzyme with extraordinarily broad substrate recognition capabilities; that is, it violates the law of enzyme specificity".

Given the central importance of the notion of "specificity" in classical biochemistry, various models were put forward to explain MDR without absolutely requiring a drug-handling activity; by characterizing the interactions between the physico-chemical properties of drugs and biophysical changes recurrent in MDR cells, i.e. involving membrane potential [10], cytosolic pH [10,11] and membrane recycling [12,13]. Although conceptually satisfying and in accordance with the notion of specificity and hence, basic laws of biochemistry, it is worth noting that these models have their own limits and that they cannot rule out completely, the involvement of drug-handling by transporters. Are we back in a conceptual dead-lock?

Not necessarily, as recent works have demonstrated that membrane changes, reflected by alteration of parameters stated above (electric potential, pH and membrane recycling), may be central to maintain drugs in the membrane for a sufficient long time and hence allow drug pumping. Indeed, if we assume that, the specificity is not central to drug pumping, the only possibility for efficient drug extrusion relies on repeated collisions between a drug and the set of membrane transporters. For example, all chemists know that increasing the temperature accelerates the reaction rate. Albeit temperature is unlikely to be directly involved as such in drug pumping, it is worth mentioning that physicists have demonstrated a similar role to diffusion in two dimensions [14,15]. This would mean that extrusion is warranted by the diffusion properties and membrane changes. Looking at the MDR problem from this angle, opens new possibilities for the development of novel therapeutic strategies.

If the membrane diffusion is so important why not targeting the membrane itself to change the ability of transporters to interact with drugs. Doing so, we would impair the drug/transporter interaction allowing more drug uptake by cells. These membrane changes that seem so important in MDR have to be related to how parasites "handle"

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their membrane, i.e. what happen to parasites' membrane when they reach the drug resistant state. Thus, if one wants to eradicate MDR, it is the membrane of parasites that needs to be focused upon and targeted by specific drugs.

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