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Dominant mechanisms of primary resistance differ from dominant mechanisms of secondary resistance to targeted therapies

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Contents

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ABSTRACT

The effectiveness of targeted therapies is currently limited, as almost all patients eventually acquire resistance within year/year and a half from therapy initiation and a small subset of a patients fail to respond at all, demonstrating intrinsic resistance. The aim of this review was to determine the potential common features and differences between the mechanisms of intrinsic and acquired resistance to targeted therapies by analyzing established resistance-generating alterations for ten FDA-approved targeted drugs. The frequency of alterations underlying intrinsic and acquired resistance shows distinctive pattern, where dominant mechanisms of intrinsic resistance include aberrations of signals downstream or upstream of the targeted protein and dominant mechanisms of acquired resistance refer to lesions in the target itself or alterations of signals at target-level that can mimic or compensate for target function. It appears that during the evolution of acquired resistance, the tumor cell is inclined to preserve the same oncogene addiction on a targeted protein it had prior to drug administration. On the other hand, intrinsic resistance develops early in tumorogenesis and is based on randomly selected mutated signals between targeted and non-targeted signaling pathways, leading to the acquisition of cancer hallmarks. In general, there is an overlap between the mechanisms of intrinsic and acquired resistance, but the occurrence frequency and distribution of alterations underlying intrinsic and acquired resistance to targeted therapies are significantly different. Focus should be placed on different group of genes in pursuing predictive markers for intrinsic and acquired resistance to targeted therapies.

1. Introduction

The introduction of targeted therapy, due to its selectivity, has raised hopes as new approach for cancer treatment and a possible solution for this devastating disease. But now, more than 15 years after its first appearance in cancer treatment, reality has forced us to ease our optimistic expectations.

Namely, nearly all FDA-approved targeted therapies in cancer treatment have the same outcome in patients: a small subset of patients (10–20%) fail to respond to therapy, demonstrating intrinsic or primary resistance and almost all patients who initially respond to therapy acquire resistance within twelve to eighteen months from therapy initiation (Ellis and Hicklin, 2009). Although a great deal of effort has been invested in elucidating the genetic background of resistance to targeted therapies, to date, no resistance biomarker has been approved that could select resistant patients from sensitive ones. However, in 2009, the American Society of Clinical Oncology has suggested that metastatic colorectal cancer (CRC) patients displaying an alteration in codon 12 or 13 of KRAS should not be considered for the monoclonal anti-EGFR therapy cetuximab (Allegra et al., 2009). It has been shown that

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approximately 40% of patients with colorectal cancer have the alteration in exon 2 of the KRAS gene, resulting in resistance to cetuximab (Imamura et al., 2012). Many other genetic alterations that contribute to resistance to targeted therapies have been found in a very small percentage of patients selected for therapy application (Turke et al., 2010; Takezawa et al., 2012; Ohashi et al., 2012). Hence, it is clear that tumor heterogeneity is also manifested in mechanisms of resistance to targeted therapy (Romano et al., 2013). Therefore, no single biomarker in resistance prediction to a particular targeted therapy can be expected. Instead, it is more likely that a prediction of resistance to targeted therapy would be more effective by introducing a group of suspected biomarkers where resistance-generating lesion(s) for every patient treated with a particular targeted therapy would be expected to be found within the narrow group of resistance biomarkers. Narrowing a group of potential biomarkers that could predict resistance to a certain therapy is another necessary step in the upcoming era of personalized cancer treatment. This type of "panel testing" has already been proposed for positive predictive biomarkers in lung cancer where analysis of a panel of potentially actionable positive biomarkers show benefit in prediction of positive response to a particular drug compared to single biomarker usage (Kim et al., 2011).

It is an interesting fact that different targeted therapies used as treatment for various types of cancers show a similar outcome, with an analogously small percentage of patients failing to respond to therapy at all, while others who respond eventually relapsing within a comparable time period. Is there some common denominator behind the resistance mechanisms to different targeted therapy? If the answer to this question is affirmative, could this knowledge be helpful in improving the prediction of resistance to targeted therapies? Hence, the aim of this review is to unravel the potential common features and differences between intrinsic and acquired resistance mechanisms by analyzing frequencies and distribution of established alterations that contribute separately to intrinsic and acquired resistance for ten FDA-approved targeted therapies: erlotinib, cetuximab, trastuzumab, lapatinib, vemurafenib, imatinib, crizotinib, everolimus, sunitinib and vismodegib.

2. Diversity of resistance mechanisms to targeted therapies

Some common features of resistance to targeted therapy have already been established, improving our understanding of the resistance process in cancer cells. In this context, mechanisms of resistance to targeted therapies can be categorized as following (Holohan et al., 2013; Pohlmann et al., 2009; Hammerman et al., 2009; Milojkovic and Apperley, 2009; Jänne et al., 2009; Summy et al., 2005):

a) mutation(s) or non-genetic alteration(s) in the target itself or other protein(s) with the effect of disabling or interfering with productive drug-target contact;
b) mutation(s) or non-genetic upregulation of the signaling component(s) that displays functional redundancy with a target and can mimic or compensate for target function;
c) mutation(s) or non-genetic up- or down-regulation of the signaling component(s) downstream or upstream of a target, resulting in activation of the targeted signaling pathway;
d) reprogramming of a cell by activation and dependence on an alternative, compensatory signaling pathway;
e) activation of a non-selective multidrug resistance (epithelial–mesenchymal transition/EMT, overexpression of ATP-binding cassette/ABC transporters, lysosomal sequestration).

Hence, there are numerous mutations and non-genetic abnormalities by which a tumor cell can develop resistance to the targeted therapy. Table 1 lists established aberrations that contribute to intrinsic and acquired resistance for the ten FDA-approved targeted therapies included in this review, based on the above mentioned categorization. Following this classification, the tumor cell can acquire an aberration on a targeted oncoprotein with the effect of disabling or hindering productive drug-target contact. These secondary target lesions usually include non-synonymous point mutation, protein overexpression or gene amplification (Inukai et al., 2006; Montagut et al., 2012; Gorre et al., 2001). A missence mutation within a target protein can cause steric hindrance for drug binding (Gorre et al., 2002), altered conformation of a target protein (Shah et al., 2002) or increased affinity for a physiological compound competing for the same drug binding site within the target (Yun et al., 2008). On the other hand, amplification/overexpression of a target produces an increased dosage of the targeted protein and a stoichiometric imbalance between a drug and a target. In addition, resistance-generating alteration on a targeted oncoprotein can result in a truncated protein formation, dysregulated target degradation or even complete loss of the targeted protein (Sperinde et al., 2010; Lu et al., 2007; Doebele et al., 2012).

Even if a targeted protein remains unaltered, gene amplification or overexpression of another protein that has the ability to mask the targeted protein can disable effective drug-target contact (Nagy et al., 2005). An activation of a protein (usually by overexpression or gene amplification) located at the target signaling level and displaying similar function with a target, can enable the tumor cell to continue to proliferate despite efficient target inactivation. In this way, due to protein functional redundancy, inactivation of a membrane receptor with a drug can be compensated by amplification or overexpression of another membrane receptor in the targeted signaling pathway, or inactivation of cytoplasmic kinase by overexpression of another cytoplasmic kinase with a similar function (Takezawa et al., 2012; Yonemori et al., 2010; Johannessen et al., 2010; Montagut et al., 2008). An activating mutation on a proto-oncogene or an inactivating mutation on a tumor suppressor located downstream or upstream of a target, can retain pathway activity despite efficient inactivation of the target (Yamamoto et al., 2008; Laurent-Puig et al., 2009; Sartore-Bianchi et al., 2009; Nagata et al., 2004; Eichhorn et al., 2008; Nazarian et al., 2010). An alteration in a downstream signal can uncouple signaling from the upstream targeted oncoprotein (Rexer et al., 2014) while an alteration affecting a signal located upstream of the target can result in a bypass of the targeted protein with an target ortholog, maintaining the signal flux through targeted signaling pathway (Nazarian et al., 2010). Further, the tumor cell can change/reprogram its oncogene addiction to the targeted signaling pathway, or develop this non-target oncogene addiction prior to therapy, through activation of another signaling pathway that can mimic or compensate for targeted pathway (Bivona et al., 2011; Huang et al., 2012; Xia et al., 2006; Turajlic et al., 2014; Chen et al., 2011). Dysregulation of a gene that directly controls apoptosis has been shown to be a very common reprogramming mechanism of resistance to targeted therapy (Ng et al., 2012; Simasi et al., 2014; Valabrega et al., 2011; Tanizaki et al., 2011; Haq et al., 2013) (see Table 1).

3. Resistance to trastuzumab indicates differences between intrinsic and acquired resistance mechanisms

Most authors addressing the differences between primary/intrinsic and secondary/acquired resistance mechanisms to targeted therapies rarely tackle this problem in a comprehensive way, commonly assuming that these two mechanisms overlap