Leukemia (2019) 33:863–883
https://doi.org/10.1038/s41375-018-0362-z

REVIEW ARTICLE

Multiple myeloma gammopathies

The future of myeloma precision medicine: integrating the compendium of known drug resistance mechanisms with emerging tumor profiling technologies

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Received: 13 August 2018 / Revised: 25 October 2018 / Accepted: 12 November 2018 / Published online: 25 January 2019

Abstract

Multiple myeloma (MM) is a hematologic malignancy that is considered mostly incurable in large part due to the inability of standard of care therapies to overcome refractory disease and inevitable drug-resistant relapse. The post-genomic era has been a productive period of discovery where modern sequencing methods have been applied to large MM patient cohorts to modernize our current perception of myeloma pathobiology and establish an appreciation for the vast heterogeneity that exists between and within MM patients. Numerous pre-clinical studies conducted in the last two decades have unveiled a compendium of mechanisms by which malignant plasma cells can escape standard therapies, many of which have potentially quantifiable biomarkers. Exhaustive pre-clinical efforts have evaluated countless putative anti-MM therapeutic agents and many of these have begun to enter clinical trial evaluation. While the palette of available anti-MM therapies is continuing to expand it is also clear that malignant plasma cells still have mechanistic avenues by which they can evade even the most promising new therapies. It is therefore becoming increasingly clear that there is an outstanding need to develop and employ precision medicine strategies in MM management that harness emerging tumor profiling technologies to identify biomarkers that predict efficacy or resistance within an individual's sub-clonally heterogeneous tumor. In this review we present an updated overview of broad classes of therapeutic resistance mechanisms and describe selected examples of putative biomarkers. We also outline several emerging tumor profiling technologies that have the potential to accurately quantify biomarkers for therapeutic sensitivity and resistance at genomic, transcriptomic and proteomic levels. Finally, we comment on the future of implementation for precision medicine strategies in MM and the clear need for a paradigm shift in clinical trial design and disease management.

Introduction

Multiple Myeloma (MM) is the second most common hematologic cancer in the United States, with over 30,000 new cases each year, and accounts for about two percent of all cancer deaths [1, 2]. MM is characterized by clonal expansion of malignant post-germinal-center B-cell-derived plasma cells within the bone marrow compartment [3, 4].

Quantitative sequencing/profiling methods developed at the advent of the post-genomic era have spurred a great number of "omics" studies aiming to unravel the complex disease biology of MM [5]. The complex, dynamic and highly heterogeneous molecular architecture of MM confers variable response to front-line therapies and underscores the development of RRMM. Large cohort studies, including a recent first-of-its-kind large-scale ($n = 765$) whole genome study, have provided a substantial body of knowledge regarding the clonal and sub-clonal heterogeneity present in MM [6–12]. The full landscape of known genomic abnormalities reoccurring in MM has recently been expertly reviewed elsewhere [13, 14].

Dynamic intra-patient (sub-clonal) heterogeneity in MM has only recently been described at great depth by a number of studies [6, 8, 10, 15–19]. It has been suggested that cases

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of high-risk disease may harbor exceptional sub-clonal heterogeneity [8, 15] that may be accelerated by DNA damaging therapies [15, 17]. Interestingly, some studies have observed that distinct sub-clones appear at alternating points along longitudinal sampling (clonal tides), suggesting they can persist below detectable levels within a patient [15, 17, 18]. This suggests that what is presumed to be "acquired resistance" at relapse may, in some cases, represent positive selection for innately resistant minority sub-clones. Some recent studies have proposed the debated concepts of MM cancer stem cells or tumor propagating cells that are alleged to be a phenotypically distinct, slow-cycling minority sub-populations that is responsible for populating the bulk tumor and harbors innate resistance to therapy [20]. Together, these observations illustrate the need to develop more sensitive methods to profile minority MM sub-clones.

It is now widely accepted that epigenetic abnormalities are abundantly present in cancer and are critically important for oncogenesis and disease progression and MM is no exception. Recent epigenetic studies in MM have described heterogeneous abnormalities in DNA methylation, non-coding RNA expression, chromatin modifications and mutations in epigenetic regulators among others [21–24].

The last two decades have seen a surge of MM "omics" studies that have refined our understanding of the complex, dynamic, and heterogeneous architecture of malignant plasma cells. Presuming that dynamic heterogeneity is the leading cause of failure to manage and overcome RRMM, there is an increasing need to identify reliable biomarkers of drug resistance and develop sensitive methodological approaches that can identify them at sub-clonal resolution.

Current and emerging myeloma therapies

MM treatment strategies have gradually evolved since the initial application of alkylating agents and corticosteroids in the 1960s that extended median survival to two years [25]. Application of high-dose melphalan followed by autologous stem cell transplantation (ASCT) by the end of the twentieth century improved median survival to 5 years [26, 27]. The additional inclusion of proteasome inhibitors and immunomodulatory drugs (IMiDs) during the last decade further elevated median survival to over 6 years [28]. The current palette of FDA approved anti-MM drugs include proteasome inhibitors (PIs: Bortezomib (BZ), Carfilzomib (CZ) and Ixazomib (IZ)), immunomodulatory drugs (IMiDs: Thalidomide, Lenalidomide and Pomalidomide), a pan-histone deacetylase (HDAC) inhibitor (Panobinostat), alkylating agents (Melphalan, Cyclophosphamide, Bendamustine), corticosteroids (Dexamethasone and Prednisone) and the recent addition [29, 30] of monoclonal antibody therapies (Daratumumab (anti-CD38) and Elotuzumab (anti-SLAMF7, CD319)) [4].

Advances in drug development over the last decade have produced a myriad of new putative anti-cancer compounds and a concomitant rise in related pre-clinical and clinical studies in MM [31–33]. These include emerging classes of therapeutics including immunotherapies that have the potential to revolutionize cancer treatment by targeting cell surface markers that may be shared among sub-clonally heterogeneous tumors. While full compendium of MM pre-clinical and clinical studies conducted over the last decade is far too vast to catalog for the purposes of this review, we provide many of the important targets that have recently been explored in pre-clinical studies and continue to be explored through clinical trials in Table 1. This rapidly expanding arsenal of anti-MM therapies presents an opportunity to improve patient outcomes while also presenting the welcome challenge of accurately selecting appropriate therapies.

Despite a three-fold improvement in median survival with the application of novel agents in recent decades, MM is still considered to be a mostly incurable disease. Nearly all patients will inevitably suffer from innate (refractory) or acquired (relapsed) resistance to front-line anti-MM therapies [34]. Drug resistance in relapsed/refractory MM (RRMM) is likely the most vexing obstacle to long-term management of MM. Given the multitude of emerging therapeutic options for MM there is an outstanding need to develop novel precision medicine strategies that pre-emptively identify therapy-specific resistance biomarkers and direct therapy towards the most efficacious alternatives. In this review, we briefly overview the growing compendium of known MM drug resistance mechanisms and discuss how recent advances in quantitative molecular tumor profiling can inform predictive algorithms to identify sensitivity and resistance to specific MM therapies.

Drug resistance in myeloma: an accumulating compendium of mechanisms

The complex, dynamic and heterogeneous nature of MM pathobiology juxtaposed with the pernicious and inevitable emergence of relapsed MM presents a significant challenge for identifying specific mechanisms of therapeutic resistance. Numerous research ventures have addressed this obstacle over the last decade by divulging well known pan-cancer drivers of therapeutic resistance and exposing many new MM-specific culprits [5]. These continually accumulating studies have made one thing abundantly clear: no one molecular marker, genotype or mechanism is universally responsible for conferring resistance to any specific therapy in MM. Furthermore, malignant plasma cells appear to have

Table 1 Targets of emerging anti-myeloma therapies in recent pre-clinical studies and recent/ongoing clinical trials

Functional category	Major molecular targets		Type of therapy	Therapeutic agents under investigation	Highest level of evaluation in MM	NCT numbers (clinical) or references (pre-clinical)
Protein homeostasis	Proteasome		Small compound	Marizomib	Phase II	NCT00461045
			Small compound	Oprozomib	Phase I/II	NCT01881789, NCT01832727, NCT02072863, NCT01416428
	E1 ubiquitin activating enzyme		Small compound	PYZD-4409	Pre-clinical	[192]
	MDM2	Human double minute 2 E3 ubiquitin ligase	Small compound	Nutlin-3	Pre-clinical	[193]
	USP9X	Ubiquitin-specific protease (deubiquitinating enzyme)	Small compound	WP1130	Pre-clinical	[194]
	USP9X and USP24		Small compound	EOAI3402143	Pre-clinical	[195]
	USP7		Small compound	P5091	Pre-clinical	[196]
	HSP90	Heat shock protein	Small compound	Tanespimycin	Phase III	NCT00546780
	HSP70		Small compound	Ver-155008, MAL3-101	Pre-clinical	[83]
Survival signaling	BCL-2	B-cell lymphoma 2	Small compound	Venetoclax	Phase III	NCT03539744, NCT02755597
PI3K/AKT/mTOR signaling pathway	PI3K	Phosphatidylinositol 3-kinase	Small compound	CUDC-907	Phase I	NCT01742988
	AKT	Protein kinase B	Small compound	GSK2141795, AZD5363	Phase II	NCT01989598, NCT02465060
			Small compound	ONC201	Phase I/II	NCT03492138, NCT02863991, NCT02609230
	mTOR	Mammalian target of rapamycin	Small compound	Temsirolimus	Phase II	NCT00079456
			Small compound	Everolimus	Phase II	NCT00618345
Ras/MAPK signaling pathway	RAF		Small compound	Sorafenib	Phase I/II	NCT00536575
			Small compound	Encorafenib	Phase II	NCT02834364
	MEK		Small compound	Trametinib	Phase I/II	NCT01476137
			Small compound	Selumetinib	Phase II	NCT01085214

Table 1 (continued)

Functional category	Major molecular targets		Type of therapy	Therapeutic agents under investigation	Highest level of evaluation in MM	NCT numbers (clinical) or references (pre-clinical)
	MEK and RAF		Small compound	RO5126766	Phase I	NCT02407509
JAK/STAT signaling pathway	JAK2	Janus Kinase	Small compound	Ruxolitinib	Phase II	NCT00639002
	JAK1/2		Small compound	INCB16562, CYT387	Pre-clinical	[197, 198]
	PIM kinase	Proto-oncogene serine/threonine-protein kinase	Small compound	LGH447	Phase I	NCT01456689, NCT02144038, NCT02160951
Cell cycle/checkpoint	CDKs	Cyclin-dependant kinase	Small compound	Flavopiridol	Phase II	NCT00047203
			Small compound	Dinaciclib, palbociclib	Phase II	NCT00555906, NCT01096342
			Small compound	SNS-032, AT7519, TG02, RGB-286638, LCQ195, SLM6	Pre-clinical	[199]
	Aurora A		Small compound	Alisertib	Phase I/II	NCT01034553
			Small compound	AT9283	Phase II	NCT01145989
	KSP	Kinesin spindle protein	Small compound	Filanesib	Phase II	NCT02092922, NCT01989325
Cytoskeleton	Microtubules		Small compound	5HPP-33, PBOX-15, STK405759	Pre-clinical	[200–202]
Epigenetic regulation	DNA methylation		Small compound	Azacitidine	Phase I/II	NCT01155583
	HDAC6	Histone deacetylase 6	Small compound	ACY-241	Phase I	NCT02400242
			Small compound	Ricolinostat	Phase I/II	NCT01583283
	CARM1	Coactivator-associated arginine methyltransferase 1	Small compound	EZM2302	Pre-clinical	[203]
	Bromodomains (BET)	Bromodomain and extra-terminal motif	Small compound	OTX015, Molibresib, CPI-0610	Phase I	NCT01713582, NCT01943851, NCT02157636
	EZH2	enhancer of Zeste Homolog 2	Small compound	UNC1999, GSK343, EPZ005687, GSK126, E7438	Pre-clinical	[204]
	BMI-1	Polycomb group RING finger protein 4	Small compound	PTC-209	Pre-clinical	[205]

Table 1 (continued)

Functional category	Major molecular targets		Type of therapy	Therapeutic agents under investigation	Highest level of evaluation in MM	NCT numbers (clinical) or references (pre-clinical)
Drug efflux	ABCA1	ATP-binding cassette transporter	Small compound	JNJ-26854165	Pre-clinical	[206]
	MDR1	P-glycoprotein	Small compound	Nelfiravir, Lopinavir	Pre-clinical	[50]
MM surface antigens	CD19		Bi-specific T-cell engager	Blinatumomab	Phase I	NCT03173430
	CD20		mAb	Rituximab	Phase II	NCT00003554
	CD38		mAb	Isatuximab	Phase I/II	NCT02812706
			CAR-T cell	Phase I		
	CD40		mAb	Dacetuzumab	Phase II	NCT00435916
	CD56		mAb	Lorvotuzumab	Phase II	NCT02420873
	CD74		mAb	Milatuzumab	Phase I	NCT00421525
	CD138		mAb	BT062	Phase II	NCT01638936
			CAR T-cell		Phase I/II	NCT03464916
			CAR Natural Killer-cell		Pre-clinical	[207]
	SLAMF7	SLAM family member 7	CAR Natural Killer-cell		Pre-clinical	[208]
	NY-ESO-1/LAGE-1	Cancer-testis antigens	TCR-engineered T cell		Phase I/II	NCT01352286
B-cell development	BTK	Bruton tyrosine kinase	Small compound	Ibrutinib	Phase II	NCT02902965
	BCMA	B-cell maturation antigen	mAb-drug conjugate	GSK2857916	Phase II	NCT03525678, NCT03544281
			CAR T-cell		Phase I/II	NCT03322735, NCT03548207, NCT03093168,
	BCMA and CD3		Bi-specific T-cell engager	BI 836909	Phase I	NCT02514239
	BCMA and CD19		CAR T-cell		Phase I/II	NCT03455972
	BCMA and TACI	Transmembrane activator and CAML interactor	CAR T-cell	AUTO2	Phase I/II	NCT03287804
Microenvironment ineractions	c-MET	Hepatocyte growth factor receptor	Small compound	Tivantinib	Phase II	NCT01447914
			Small compound	Cabozantinib	PhaseI/II	NCT01866293
	IL-6	Interleukin 6	mAb	Siltuximab	Phase II	NCT00911859, NCT00911859
	VEGF	Vascular endothelial growth factor	mAb	Bevacizumab	Phase II	NCT00473590, NCT00464178, NCT00410605, NCT00022607, NCT00482495

Table 1 (continued)

Functional category	Major molecular targets		Type of therapy	Therapeutic agents under investigation	Highest level of evaluation in MM	NCT numbers (clinical) or references (pre-clinical)
	BAFF	B-cell activating factor	mAb	LY2127399	Phase II	NCT01602224
	RANKL	Receptor activator of NF-κB ligand	mAb	Denosumab	PhaseIII	NCT00330759, NCT01345019
	DKK1	Dickkopf	mAb	BHQ880	Phase II (smoldering myeloma)	NCT01337752
	APRIL	A proliferation-inducing ligand	mAb	BION-1301	Phase I/II	NCT03340883
	IGF1R	Insulin-like growth factor receptor	mAb	Figitumumab, Dalotuzumab, AVE1642	Phase I	NCT01233895, NCT01536145, NCT00701103
Cell Adhesion	CD44/VLA-4	Integrin α4β1	Peptide	Cyclized HYD1	Pre-clinical	[209]
	FAK	Focal adhesion kinase	Small compound	VS-4718	Pre-clinical	[210]
Nuclear export	XPO1	Exportin	Small compound	Selinexor	Phase II	NCT02336815
Anti-angiogenesis	MMPs and VEGF	Matrix metalloproteinases and vascular endothelial growth factor	Small compound	Neovastat	Phase II	NCT00022282
Immune Checkpoint	PD-1/PD-L1	Programmed cell death and programed cell death ligand 1	mAb	Pembrolizumab	Phase III	NCT02576977
			mAb	Nivolumab	Phase I/II	NCT03292263
			mAb	JNJ-63723283	Phase II/III	NCT03357952

This table is not intended to provide a complete catalog of every compound that has been evaluated in MM-related pre-clinical/clinical research studies but rather provides major examples that demonstrate the breadth of emerging molecular targets for MM therapy. Furthermore, clinical trials evaluating novel combinations of approved therapies are not listed here and some of the trials referenced here include combinations with approved MM therapeutics (trial details can be found at ClinicalTrials.gov). Some therapeutic agents listed have additional or therapeutically significant secondary targets that are not described here. *CAR* chimeric antigen receptor, *TCR* T cell receptor

a multitude of molecular avenues by which they can escape therapy.

Successful implementation of precision medicine strategies must be founded on a complete and frequently updated catalog of drug-specific biomarkers that reliably and prospectively pinpoint RRMM. For the purposes of this review, we will not delineate the entire spectrum of putative resistance mechanisms identified by countless pre-clinical studies conducted in recent decades. Rather, we provide an updated overview of known classes of MM-specific resistance mechanisms (schematically represented in Fig. 1) and describe many potentially actionable examples of resistance biomarkers. The following sections overview pre-clinical studies that employ a variety of methods, some of which go to greater lengths to model the MM microenvironment and therefore may represent a spectrum of clinical accuracy. Despite this, it is our opinion that the compendium of pre-clinical evidence, described through examples below, provide an important base of knowledge that can be translated into the clinic as supporting evidence accumulates.

Broad resistance mechanisms: pharmacokinetics and drug efflux

Drug resistance mechanisms are classically thought to relate to the pharmacodynamics of a therapeutic agent at or within the target cell type. Inter-patient pharmacokinetic heterogeneity, however, represents an underappreciated determinant of therapeutic efficacy. Variants (genomic or otherwise) that regulate the metabolism of a therapeutic compound or the rate at which it is effluxed from target cells can restrict therapeutic efficacy by not sustaining an effective concentration in target cells or by unduly elevating somatic concentrations and concomitant toxicity. Identifying variants that can predict adverse drug reactions embodies the field of pharmacogenomics. Research in the field of pharmacogenomics has made great strides in identifying common modulators of drug metabolism/efficacy [35] and compiling this information into accessible databases (i.e., PharmGKB [36]). Recent research in MM (and other cancers with overlapping therapies) has revealed promising pharmacogenomic variants relating to some MM therapies [37–42]. For example, a single nucleotide polymorphism (rs4240803) within *SLC7A5*, a gene encoding an amino acid transporter (LAT2) that facilitates melphalan uptake, was found to significantly associate with gastronomical toxicity induced by high-dose melphalan treatment in MM patients [43].

Multidrug resistance can be caused by the aberrant expression of efflux transporters that actively expel therapeutic compounds from malignant plasma cells. Several members of the ABC superfamily of transporters including P-glycoprotein (MDR1) have been specifically implicated in MM drug-resistance. While MDR1 appears not to be expressed in MM cells at diagnosis, therapy has been shown to induce its upregulation [44, 45]. Furthermore, many drugs currently used in MM therapy are known substrates for MDR1 (i.e., IMiDs and alkylating agents) and proteasome inhibitor efficacy (bortezomib and carfilzomib) has been shown to be directly affected by MDR1 expression [46–48]. High expression of the seine/threonine kinase NEK2 has been shown to contribute to MM drug resistance, in part, by acting upstream of ABC transporter expression [49]. In the future, screening for indicators of aberrant efflux activity may direct therapy towards efflux inhibitors that currently demonstrate pre-clinical efficacy in MM [50]. Despite accumulating findings in this area, translational efforts to routinely apply this knowledge towards precision medicine in MM have been virtually non-existent.

Broad resistance mechanisms: microenvironment interactions

MM is well understood to exploit complex interactions with numerous cell types within the bone marrow microenvironment to evade therapy and the host immune system [51–53]. The relationship between MM and its microenvironment is bi-directional and propagates resistance to therapy by agonizing pro-survival/anti-apoptotic mechanisms.

Environment-mediated drug resistance (EM-DR) is a result of paracrine interactions between MM cells and the microenvironment. Specifically, these interactions involve secretion and uptake of soluble factors (chemokines, cytokines, and growth factors) as well as exosomes (exocytotic nanovesicles that harbor oncogenic mRNA, miRNA and proteins). The IL-6 cytokine, secreted by the microenvironment and MM cells, is one of the best studied examples of MM EM-DR [54, 55]. IL-6-related signaling promotes therapeutic resistance by directly agonizing receptor-mediated activation of JAK/STAT, MAPK, and PI3K/AKT pro-growth/survival signaling cascades while also indirectly activating angiogenesis (via VEGF). Other soluble factors that promote pathogenic paracrine/autocrine signaling exhibit heterogeneous expression patterns have druggable downstream factors that may represent actionable biomarkers for MM EM-DR. For example, hepatocyte growth factor (HGF) upregulation in bone marrow and MM cells agonizes the pro-growth HGF receptor (c-MET) in an paracrine/autocrine loop to drive MM proliferation [56]. Resistance promoted by insulin-like growth factor signaling (IGF-1/IGF-1R) may be counteracted by directly targeting MM-expressing IGF receptors [57] or by blocking downstream signaling through AKT [58]. Expression of Bruton's tyrosine kinase (BTK), a druggable intermediate signaling component between B-cell receptor (BCR)/PI3K signaling and downstream drivers of survival (e.g., MAPK, NF-κB,

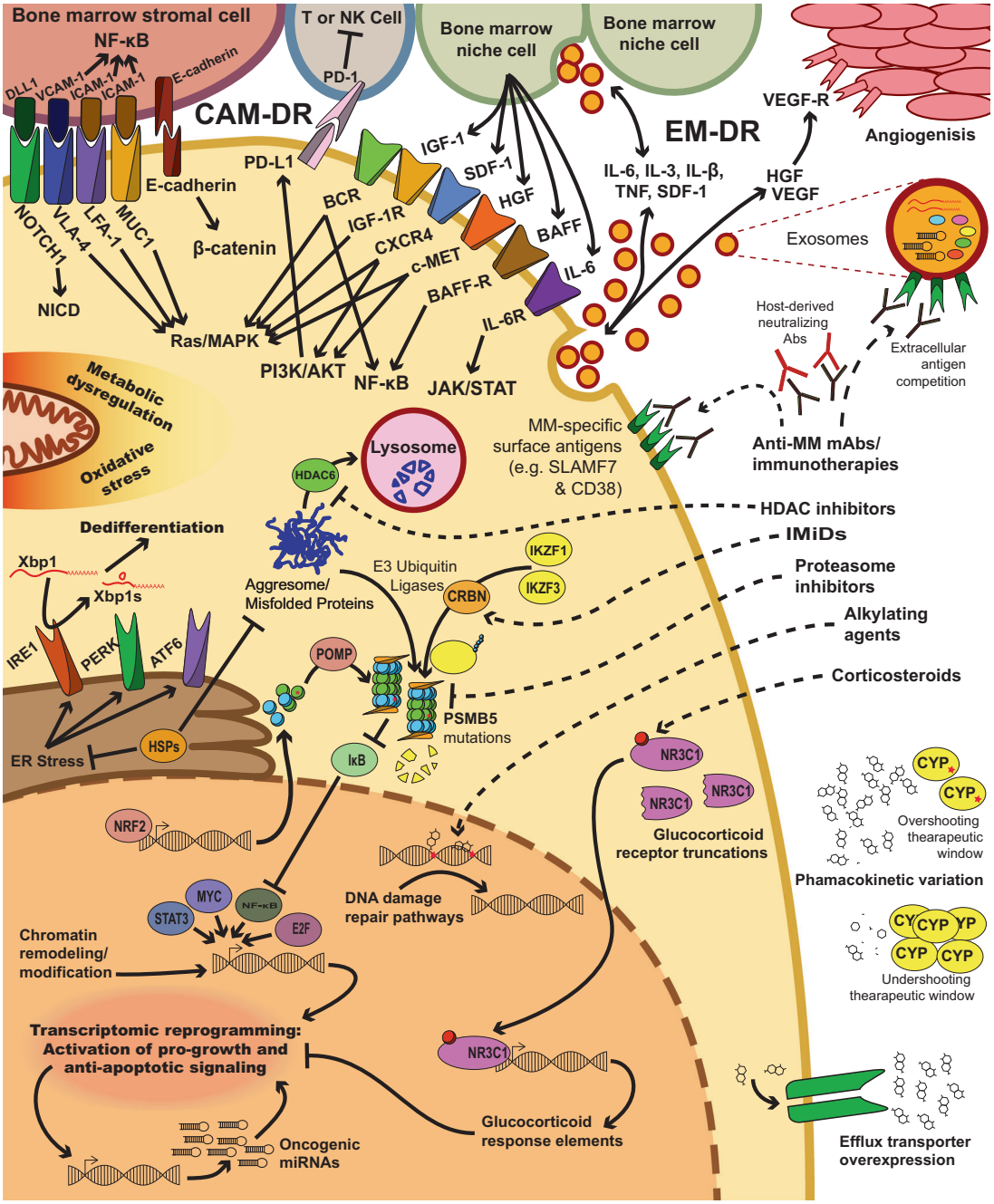

Fig. 1 A schematic representation of the currently known mechanisms of resistance to emerging and standard of care MM therapies. Represented mechanisms include pharmacokinetic variance, aberrant efflux transporter activity, truncations/mutations in drug targets, epigenetic dysregulation, DNA damage repair in response to alkylating agents, dysregulation of ubiquitin proteasome system (UPS) components, modulation of endoplasmic reticulum (ER) stress by heat shock proteins (HSPs), lysosomal clearance of aggresomes to evade ER stress, dedifferentiation, metabolic/oxidative stress response dysregulation, extracellular MM-specific antigens, host-derived neutralizing antibodies blocking efficacy of therapeutic monoclonal antibodies (mAbs), environment-mediated drug resistance (EM-DR), and cell-adhesion mediated drug resistance (CAM-DR)

and ERK), directly confers resistance to anti-MM compounds [59]. High CXCR4 expression in MM cells facilitates positive feedback between MM and stromal cells through the CXCR4/SDF-1 axis, driving cell adhesion and secretion of other soluble pro-survival/angiogenic factors (i.e., IL-6 and VEGF) [60]. This interaction can be blocked by pharmacological targeting of CXCR4 or SDF-1 [61]. Pro-survival tumor necrosis factor family cytokines BAFF and APRIL are secreted by the MM tumor microenvironment [62] and have both recently been shown to drive EM-DR by agonizing BAFF receptors (BCMA and TAC1) expressed on MM cells [63, 64].

Exosomes, like soluble factors, facilitate bi-directional crosstalk between MM and bone marrow cells that can drive EM-DR by delivering cargo that agonize pro-survival pathways [65]. While MM-derived exosomes are mostly attributed to maintaining a favorable proliferative niche in vivo [65, 66], microenvironment-derived exosomes deliver diverse tumor-supporting molecules (e.g., human mesenchymal stem/stromal cell exosomes harboring miRNAs-21 and 34a [67]) and can promote MM cell proliferation, survival and resistance to BZ [68]. Blocking exosomal release may be an advantageous avenue as MM-derived-exosomes can present MM-associated surface markers that reduce the yield of antibody-based sorting of MM cells (i.e., CD138) and efficacy of antibody-based therapy [69].

MM-microenvironment interactions can also drive resistance via cell adhesion-mediated drug resistance (CAM-DR) [53]. CAM-DR also dives resistance primarily through activation of pro-survival pathways (i.e., NF-κB) and induction of soluble factor secretion (e.g., IL-6). High cell surface expression of CAM-DR-related integrin family members may have the potential to serve as biomarkers for extreme levels of MM CAM-DR [53]. Binding between MM cell Notch receptors and stromal-cell-bound ligands has been shown to promote resistance to melphalan through pro-survival Notch signaling [70].

Recent studies describing EM-DR and CAM-DR provide a consensus that crosstalk between MM cells and their microenvironment converge on critical proliferation/survival pathways that can directly affect chemotherapeutic efficacy. This highlights a profound need to design preclinical evaluations of putative therapeutic agents that recapitulate this context.

Therapy-specific resistance mechanisms: proteasome inhibitors

Proteasome inhibitors (PIs) are among the most widely used therapies to treat newly diagnosed MM [71]. All currently approved MM PIs target the chymotrypsin-like proteolytic activity of the PSMB5 proteasomal subunit [72]. CZ has demonstrated improvement over BZ in a clinical setting, possibly due to increased potency and a more tolerable therapeutic window [73].

The proteasome is a large proteolytic holoenzyme that senses and controls a myriad of cellular processes as a component of the ubiquitin proteasome system (UPS) [72, 74]. Malignant plasma cells are thought to be uniquely sensitive to proteasome inhibition because plasma cells produce and secrete high quantities of immunoglobulin (Ig) proteins, have accentuated endoplasmic reticulum (ER) and are uniquely sensitive to any ER-stress (perturbation in protein turnover capacity) [75, 76]. Additionally, MM cells exploit certain pathways that require the UPS to complete a signaling cascade. Examples of such signaling pathways include those related to pro-survival (NF-κB), cell cycle (p21, cyclins, and p27Kip1), oncogenesis (p53 and bax), apoptosis (Bcl-2, XIAP, cIAP) and transcriptional regulation (c-Jun, E2F1, beta-catenin) [75].

PI drug resistance is an intensively studied subject areas in MM research [77]. Functionally significant *PSMB5* point mutations have only very recently been described to be present in a small number (~1%) of RRMM cases (virtually never detected at diagnosis) [78]. PSMC6 loss and/or PSMB5 overexpression have also been suggested to confer PI resistance in MM [79]. NRF2-mediated overexpression of proteasome maturation protein proteassemblin (POMP), proteasome assembly chaperone, has been attributed to PI resistance in MM cell lines [80]. Recent proteomic profiling of PI resistance in patient samples identified 188 differentially expressed proteins that included the upregulation of 16 UPS-/ER-stress-related proteins (8 proteasome subunits) [81]. MM cells can additionally circumnavigate PI-induced ER stress by clearing misfolded proteins through autophagic clearance of aggresomes through the lysosome. Blocking this mechanism was part of the impetus for adopting HDAC inhibitors to treat RRMM [82].

Heat shock protein upregulation (HSPs) aids maintenance of protein homeostasis by facilitating protein folding [83]. Treatment-induced upregulation of HSPs including Grp78, HSP90, HSP70, and HSPB8 (some of which are druggable) has been attributed to PI resistance [81, 84–86].

Metabolic dysregulation is now fully appreciated to be core hallmark of cancer and frequent mechanism of therapeutic resistance [87]. Putative metabolism-related resistance biomarkers have demonstrated enrichment in hypoxia signaling (HIF1A) [88], lactate catabolism (LDHA) [88], and serine synthesis (PHGDH) [89]. A recent differential proteomics study identified numerous differences in potentially predictive metabolic regulators between PI sensitive and resistant cell lines, including those enriched within the respiration, glycolysis, metabolite production, amino acid metabolism, nucleic acid metabolism, cofactor metabolism, fatty acid biosynthesis, protein catabolism, redox control, and glutathione regulation [90]. Proteomic changes in oxidative stress related genes have also been described in PI-resistant MM [81]. Among those, TXN and TXNDC5 overexpression have been attributed to PI therapy resistance in other MM studies [91–93] and may serve as potential therapeutic targets and/or biomarkers for oxidative-stress-related PI resistance.

Dedifferentiation of malignant plasma cells confers resistance to PIs by inducing molecular and morphological changes that reduce MM's inherent sensitivity to ER stress (i.e., reduction of the secretory apparatus/ER). This low-secretory B-cell-like phenotype has been observed in MM

and attributed to PI resistance [94, 95]. Xbp-1, a transcription factor required for terminal differentiation into plasma cells, is expressed normally in untreated bulk MM tumor samples. In B-cell-like RRMM however, Xbp-1 is frequently under expressed or absent [90, 94]. Blocking Xbp-1 splicing via IRE1α inhibition has also been shown to sensitize MM cells to proteasome inhibitors [96]. MM dedifferentiation may also be facilitated by stromal-cell-induced retinoid signaling (via CYP26 upregulation) stimulated by MM cell Hedgehog paracrine signaling (via SHH ligand secretion) [97]. Stromal CYP26 expression and/or MM SHH secretion may serve as biomarkers for this mechanism.

Therapy-specific resistance mechanisms: alkylating agents

Alkylating agents (genotoxic DNA inter-strand cross-linkers) approved for use in MM include melphalan and cyclophosphamide. Alkylating-agent-specific resistance mechanisms identified in MM are nearly exclusively confined to DNA repair pathways. The Fanconi anemia (FA)/BRCA DNA repair pathway, which specifically removes inter-strand cross-links, was the first attributed to alkylating agent resistance via upregulation of FA components (BRCA1, BRCA2, FANCA, FANCC, FANCF, FANCL, and RAD51C) [98]. More recently putative biomarkers for melphalan resistance have been expanded to include PARP1 (base excision repair (BER) and double stranded break repair (DSBR)), ATR/ATM (DNA damage signaling), XRCC4/LIG4 (NHEJ repair) and NEIL1/UNG2/MPG (BER) [99, 100]. PARP inhibitors may be able to interdict this mechanism of melphalan resistance [100]. A recent report demonstrates that recurring 1q21 amplification seen in MM drives elevated DNA repair capacity through ILF2 overexpression [101].

Therapy-specific resistance mechanisms: corticosteroids

The corticosteroids prednisone and dexamethasone are among the oldest and most widely applied MM chemotherapeutic agents that target lymphoid cells by agonizing glucocorticoid receptors (GRs). These activated GRs can activate signaling cascades at the cell membrane (e.g., MAPK) [102] or canonically recruit coregulators that transcriptionally regulate glucocorticoid response elements (GREs) that, in part, induce intrinsic apoptosis suppress proliferative/survival pathways (e.g., NF-κB) [103, 104]. Truncations in the GR-encoding gene *NR3C1* have been reported that confer corticosteroid resistance [105, 106]. Dysregulation of intrinsic apoptosis and hormone signaling pathway components have also been implicated in corticosteroid resistance (i.e., GSK3, AKT, and BIM) [103]. A recent study that describes the strongest interacting GR coregulators in a corticosteroid sensitive MM cell line and sensitive/resistant AML cell lines suggests that expression and activation of certain coregulators may dictate the context for corticosteroid efficacy in lymphoid malignancies [107].

Therapy-specific resistance mechanisms: immunomodulatory drugs

MM-approved IMiDs (thalidomide and its two modern analogs lenalidomide and pomalidomide) combat myeloma through immune activation and inactivation of angiogenesis and proliferation. The E3 ubiquitin ligase cereblon (CRBN) and its two complex partners (DDB1 and CUL4B) were recently discovered to be an essential component of MM cell response to IMiDs through its regulation of two B-cell transcription factors (Ikaros (IKZF1) and Aiolos (IKZF3)) [108]. In the wake of this discovery several IMiD-specific mechanisms have been identified including certain genes harboring recurring mutations in RRMM: *CRBN, CUL4B, IKZF1*, and *IKZF3* [109, 110] One very recent study has demonstrated that combined inhibition of epigenetic regulators (EZH2 and DNA methyl transferase inhibitors) may be able to target CRBN-mutant RRMM by downregulating IKZF1/IKZF3 in a CRBN-independent manner [111]. CRBN expression level may be the most reliable biomarker for IMiD efficacy [112–114] and upstream regulators of its protein turnover (i.e. CSN9 signalosome complex) have also been identified [115].

Therapy-specific resistance mechanisms: new and emerging immunotherapies

Emerging anti-MM immunotherapies largely act through recognition of MM-specific antigens and indeed, in the case of the recently approved monoclonal antibody (mAb) daratumumab (anti-CD38), low CD38 expression prior to or induced by daratumumab treatment affects efficacy [116, 117]. All-trans retinoic acid may be a means to overcome this resistance mechanism through rescue of CD38 surface expression and enhanced complement-dependent cytotoxicity [118]. Another mAb resistance mechanism currently only described for elotuzumab (anti-SLAM7, CD319) is the production of neutralizing antibodies by the host that target the therapeutic mAb [119, 120]. Resistance to both mAbs may be facilitated by expression of soluble, extracellular MM antigens that stoichiometrically reduce MM-cell targeting [121, 122].

Complex resistance mechanisms: epigenetics

Abnormal epigenetic changes have increasingly become understood to confer a source and/or vehicle for

therapy-specific and non-specific resistance in MM [22, 23, 82]. Therapies targeting epigenetic regulators (i.e., DNA methyl transferases, MM set domain methyltransferase (MMSET/WHSC1) and polycomb complexes) that confer higher order control over cellular "stemness" (activated proliferative/anti-apoptotic pathways) may have the potential to broadly target malignant plasma cells regardless of resistance to front-line therapy [111, 123–125]. Many of these epigenetic targets also regulate expression of key MM transcription factors related to drug-resistance (e.g., MYC and FOXM1) for which there are no direct inhibitors [22, 123]. MiRNAs have been shown to be differentially regulated, in part, by other aberrantly active epigenetic regulators and may represent one of the most easily quantifiable aspects of the epigenetic landscape [126]. While oncogenic miRNAs are mostly described as modulators of oncogenic/tumor suppressor pathways, many have also recently been shown to regulate many of the molecular factors critical for the specific resistance mechanisms outlined above [82, 127].

Current methods in clinical profiling of MM: molecular classification and risk assessment

Despite the vast compendium of accumulating knowledge related to MM resistance mechanisms, there has been little effort to routinely integrate this information into clinical decision making. This, however, is not to suggest that molecular profiling is not a routine aspect of MM disease management. Current profiling methods employed in MM serve predominantly to inform the molecular classification of MM cases and to provide a prediction of risk/prognosis.

The most widely utilized profiling methods, metaphase G-banded karyotyping and fluorescence in situ hybridization (FISH), quantify common MM-specific cytogenetic abnormalities. FISH analysis may be sufficient to stratify risk in MM [128], but rarely provides reliable, drug-specific predictions for efficacy (notable exceptions include trisomies that predict exceptional response to lenalidomide-based therapy and t(4;14) that responds best to BZ-based therapy [129]). Several groups have used gene expression profiles (GEPs) in conjunction with cytogenetics to cluster and describe at least 10 MM subgroups that have significantly distinct clinical features/outcomes [130–132]. These molecular classification studies have illuminated disease subtypes that are distinguished by specific molecular features including recurrent cyclin D translocations, cyclin D expression, hyperdiploidy (including specific trisomies), MAFB/c-MAF activating translocations, MMSET-activating translocations, overexpression of NF-κB pathway genes, overexpression of cancer testis antigens (CTAs) and overexpression of specific tyrosine phosphatases (e.g., PRL-3) [130–132]. These prognostic classifications, considered in combination with additional clinical data, have been evaluated and incorporated into a consensus statement compiled by the International Myeloma Working Group (IMWG) [133]. Clinically, this prognostic information has been incorporated into routine disease management as widely used risk stratification models including the revised International Staging System (RISS) [134] and risk-adapted strategies including the Mayo Clinic's updated mSMART consensus guidelines [135].

The advent of post-genomic era technologies spurred many research groups to evaluate the prognostic value of microarray-based GEPs. The first prognostic MM-specific GEPs were derived from patient samples and myeloma cell lines by several MM research groups UAMS [136], IFM [137], INSERM [138], and HOVON [139]. Additional published MM-specific prognostic GEPs are tailored to specific prognostic phenomena including centrosome index, cell death, chromosome instability, and proliferation signatures [140–143].

Identifying high-risk MM may have some clinical value, however we ardently assert that the ultimate goal of predictive transcriptomics should not be to only offer general prognosis. Rather, this approach should also direct rational choices between the growing palette of MM therapeutic options. Moreover, we feel that there is a pressing need to integrate drug-specific resistance biomarkers with several very promising emerging quantitative molecular profiling technologies (schematically represented in Fig. 2).

Emerging methods in clinical profiling of MM: DNA sequencing for clinical genomics

Large scale clinical studies employing next generation sequencing (NGS) and FISH have compiled a compendium of recurring MM-associated genomic abnormalities including translocations, copy-number variations (CNVs) and non-synonymous single nucleotide variations (SNVs) (median 60 exonic mutations with a wide range from 10 to 500+ [144]) [14]. High-resolution NGS has substantial potential clinical utility as it can simultaneously survey MM-associated translocations, CNVs, SNVs, and allelic/clonal fractions.

Several recent studies have pioneered much more feasible targeted sequencing approaches for NGS in MM [9, 19, 109, 145–147]. Additional recent targeted NGS efforts have conducted longitudinal sub-clonal analysis [144] and have provided methods for an established targeted sequencing panel (M^3P) [148]. Unlike WES, targeted NGS panels could potentially screen recently described SNVs recurring within the non-coding MM genome fraction [12].

A recent study describes a model for the MM sub-clonal landscape that exhibits dynamic special heterogeneity, implying that current bone marrow sampling procedures

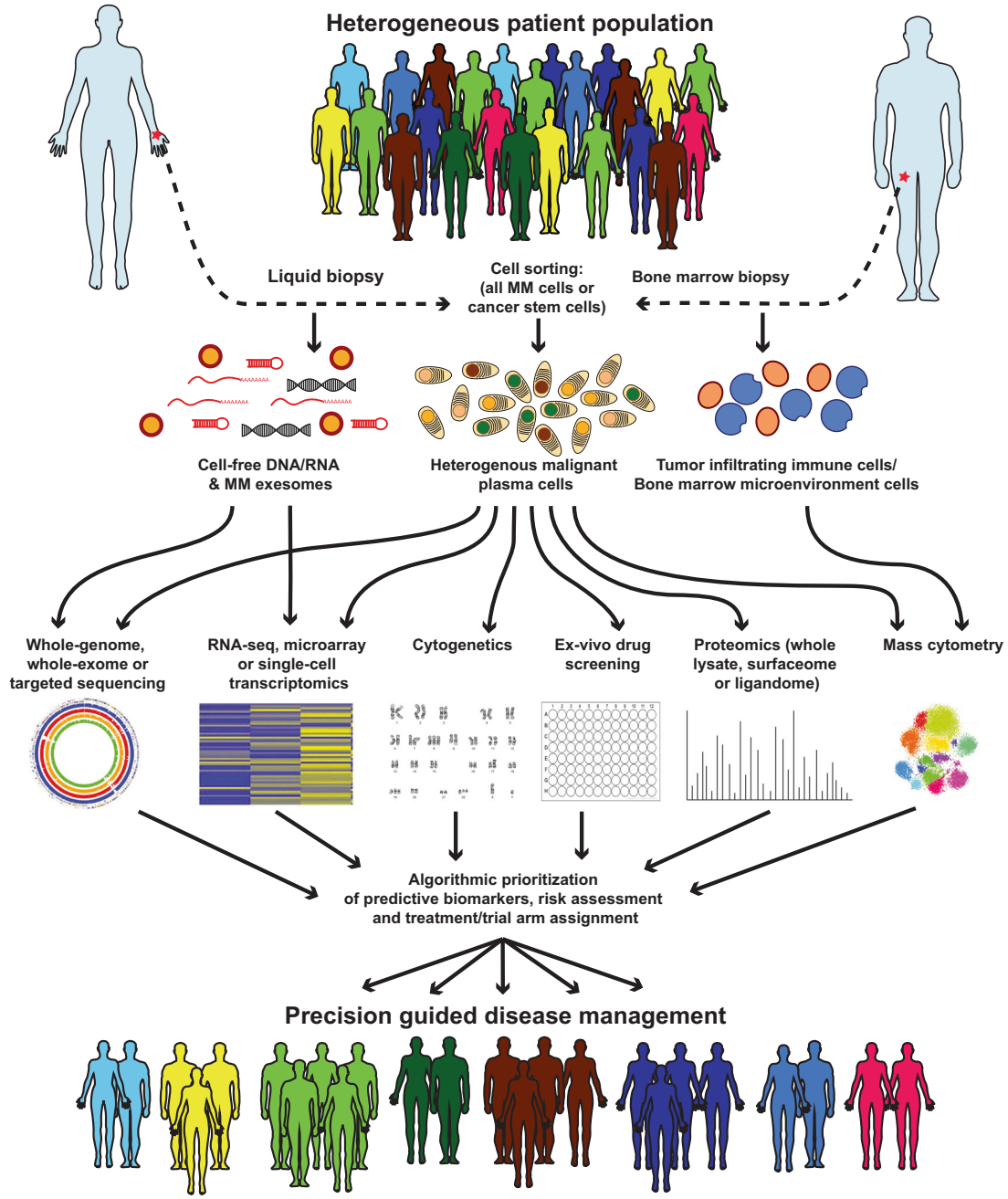

Fig. 2 A schematic representation of emerging technologies applicable to precision medicine in MM disease management. Emerging methods of quantitative tumor profiling present a number of promising options towards the accurate identification of biomarkers for therapeutic efficacy and failure that can direct therapy and clinical trial arm assignment

may inaccurately represent the sub-clonal architecture present in an individual due to focal sampling bias [149]. Additionally, increasing interest in incorporating molecular profiling into longitudinal monitoring of minimum residual disease [150–152]) also presents a feasibility-based need to find alternatives to repeated bone marrow biopsies. Momentum has therefore increasingly accumulated behind using liquid biopsies to sample peripheral blood and quantify circulating tumor cells (CTCs) and cell-free/circulating tumor DNA (ctDNA). Recently, landmark studies pioneering various NGS-based methods to profile bone marrow and liquid biopsies (CTCs and/or ctDNA) from the same patients yielded liquid-biopsy-based mutational profiles that nearly perfectly matched (and in some cases exceeded) the sensitivity of bone marrow profiling [153–156]. Digital droplet polymerase chain reaction (ddPCR) has also been used to profile ctDNA with extremely high sensitivity [157, 158].

Emerging methods in clinical profiling of MM: RNA sequencing

Clinical translation of gene expression profiles (GEP) in MM has been restricted to predicting prognosis. Despite this, accumulating descriptions of substantial therapy-induced epigenetic and transcriptomic changes suggest that RNA profiling may be an effective means to clinically screen for resistance biomarkers.

Circulating MM-associated miRNAs are demonstrating increasing potential as reliable biomarkers for drug resistance as they are the most stable RNA species, demonstrate greater serum abundance than ctDNA and can, individually or as an ensemble, convey a wealth of regulatory information [82, 127]. Recently, studies quantifying circulating miRNAs in MM patients identified differential expression signatures between responders and non-responders to lenolidamide/dexamethasone combination therapy [159] and BZ-based therapy [160]. Changes in miRNA expression have also been characterized longitudinally throughout plasma cell differentiation and may therefore be potentially useful in screening for dedifferentiation-induced PI resistance [161].

Drug-resistance mRNA-based GEPs were first described using microarrays to measure kinetic (drug-induced) transcriptomic responses to PIs. The first instances of this approach included an 80-gene kinetic (treated relative to untreated control) GEP derived from patients before and after BZ-treatment [162]. Using a murine MM model, we identified 23-gene PI-resistance signature that successfully stratified clinical data [163]. Other approaches have used microarray analysis between extreme responders and non-responders to develop weighted scoring model for resistance prediction to HDAC and DMT inhibitors [164, 165]. Inspired by these studies, we recently systematically profiled cytotoxic responses of 50 myeloma cell lines to four PIs. Transcriptomic differences between sensitive and resistant cell lines identified a 42-gene GEP that successfully stratified patient outcome exclusively in PI-treatment-containing arms of all clinical trials examined, suggesting translational significance and drug-specificity [166]. A recent data mining study described a 14-gene-based scoring system that successfully stratified clinical response to IMiDs [167].

Single-cell transcriptomic technology (targeted/qPCR or RNAseq) is still in its infancy and suffers from inherent technical difficulties [168]. It is, however, being rapidly developed [169] and holds great potential for utility in MM precision medicine. The first published use of single-cell RNAseq in MM was able to distinguish MM CTCs from healthy plasma cells and demonstrated that single-CTC transcriptomes were representative of bulk bone marrow sample transcriptomes [153]. We recently published a proof-of-principle study that employed single-cell targeted RNA quantification in conjunction with a novel bioinformatics pipeline Single-Cell Analysis of Targeted Transcriptome (SCATTome: https://github.com/bvnlabSCATTome) that filters, imputes, and scales data prior to machine-learning-based generation of weighted PI resistance scores for individual cells [170]. This study demonstrated that single cell analysis of cell lines and patient samples via SCATTome can accurately stratify PI response in MM cell lines and patient outcomes. This study additionally describes drug sensitive cell lines that harbor minority single cells with high resistance scores.

Emerging methods in clinical profiling of MM: clinical proteomics and quantitative immunoassays

The most immediate interest translating mass spectrometry (MS) to MM management is in its potential to monitor MRD through quantification of clonal serum Ig as a proxy for disease burden [171]. MS-based approaches to profile protein abundance and/or modifications in bone marrow and serum samples have provided invaluable insights into the functional/regulatory differences between different levels of chemoresistance that are not conveyed through DNA/RNA [81, 90, 92, 172]. MS-based chemoproteomics has demonstrated potential to resolve unknown pharmacodynamics interactions with emerging therapeutics [173]. MS-based characterization of MM-associated neoantigens or the "HLA ligadome" has demonstrated feasibility and may eventually be invaluable to directing immunotherapy in individual cases [174]. MS-based methods to quantify specific post-translation modifications have immense potential utility as exemplified in recent phosphoproteomic profiling of downstream FGFR3 pathway activation as a biomarker for MM drug-resistance [175].

Numerous non-MS methods for protein quantification have also been employed in MM. Capillary nano-electrophoresis with immunoassay (CNIA) has demonstrated extreme sensitivity with miniscule sample quantities and clinically accurate predictions for IMiD response based on CRBN pathway member protein abundance (where RNA failed to accurately predict) [176]. A different, highly multiplex-amendable immunoassay (MAGPIX®) was recently used to characterize kinetic proteomic changes induced by BZ [177]. Protein arrays were recently used to implicate serum extracellular vesicles harboring MM-associated CD44 as a chemoresistance mechanism [178].

One of the most intriguing potential utilities of proteomic profiling is to quantify the vast cell-surface proteome or "surfaceome" (representing 30% of the genome) that mediates direct/indirect cell-to-cell interactions, receptor signaling, drug efflux, presentation of MM-specific antigens for immunotherapy; all of which is not accurately predicted

from genomnic/transcriptomic quantification [179]. MM therapy-associated surfaceomics has yet to be addressed in current literature.

Flow cytometric analysis has a well-established role in quantifying/monitoring MM via highly sensitive, antibody-based, single-cell protein quantification [150]. Flow cytometry to a certain extent, is amendable to multi-plexing (multi-color flow: FBC). Multi-parameter fluorochrome-based cytometry is inherently confined to a detection maximum of about ten antigens due to limited spectral real-estate. A relatively new cytometric method, mass cytometry or cytometry by time-of-flight (CyTOF), overcomes the technical limitations of FBC by detecting heavy-metal-ion-conjugated antibodies through time of flight mass spectrometry, raising the targetable antigen limit to near 40. The first published example of CyTOF applied to primary MM samples molecularly and computationally dissected the immune cell constitution of peripheral blood mononuclear cells to expose an abnormally expanded non-malignant memory B cell phenotype [180]. A MM-specific CyTOF protocol for deep profiling of individual patients' immune system has been recently published [181]. We recently published an immunophenotypic dissection of an isogenic MM cell line pair (PI-resistant and PI-sensitive) [182]. In this study we compared CyTOF and FBC output and found that CyTOF demonstrated a clear advantage through more robust identification of factors that distinguished the isogenic cell lines and, encouragingly, a sub-clonal architecture in the sensitive line that harbored a minority fraction of resistance-like cells. This proof-of-principal study presents an important demonstration of the profound profiling capability that CyTOF can offer by simultaneously quantifying multiple aspects of the MM proteome [182].

Emerging methods in clinical profiling of MM: ex-vivo drug screening

High-throughput drug screening is another pre-clinical approach that has demonstrated significant capacity for discovery in pre-clinical drug-resistant MM cell lines [183]. A small number of MM studies have recently pioneered a novel approach to precision medicine: ex-vivo "direct to drug" screening. This approach samples a primary bone marrow biopsy for immediate high-throughput cytotoxic analysis. Two recent studies in MM that employ this technique (one currently ongoing) report/preview findings that are rich with sensitivity data matched with cytogenetic classifications and patient outcomes [184, 185]. As expected, these patient populations exhibit widespread heterogeneity in response to the applied panel of compounds. Majumder et al. clustered patients based on their ex-vivo cytotoxicity profiles and noted a surprising observation that the most drug-sensitive group (also enriched for standard risk prognosis) had the worst overall outcome, suggesting that the broad sensitivity highlighted by activation of multiple drug-targetable oncogenic pathways conferred highly aggressive disease in the absence of targeted therapeutics. Only three patients with advanced stage disease had therapy directed by their ex-vivo cytotoxicity profiles in this study. These cases demonstrated good correlation between *ex-vivo* and in-vivo response. This study additionally suggested that patients harboring the poor prognosis marker del(17p), resulting in deletion of *TP53*, may benefit from HDAC or BCL2 inhibition based on ex-vivo responses [185]. A similar study conducted in hematologic malignancies (not including MM) also employed ex-vivo sampling and cytotoxic profiling [186]. In this study patients were either subjected to ex-vivo profile-informed disease management or "physicians choice" disease management (17 patients each). This study is distinct from the aforementioned MM studies in that the authors of this study employed "pharmacoscopic" analysis: a systematic high-throughput single-cell imaging/computational analysis pipeline (testing 768 conditions in nearly all patients with a 5 day turnaround). This study, despite having a small cohort size and some notable confounding factors in several individual cases, yielded very favorable results that support expansion of trials that randomize between pharmacoscopy-guided and physician-chosen therapies. Moreover, the authors of that study posit that effective therapeutic options already exist for the majority patients, even those with multiple relapses, however a lack of precision medicine prevents those patients from receiving the most efficacious treatments.

Ex-vivo screening methods are also being developed that harness recent technological advancements that culture primary samples using systems that are much more accurately reflect the natural tumor environment and therapeutic response. Two examples include in-vitro microfluidic co-culture assays (MicroC3) [187] and in-vivo avatars or patient derived xenograft assays (PDX) [188, 189], both of which are being incorporated into future MM precision medicine trials [190].

Concluding thoughts on the future of precision medicine in myeloma: barriers to implementation and the need for a paradigm shift in clinical trial design

The post-genomic era has been a fruitful period of discovery in MM research. Various large scale 'omics' studies undertaken in the past decade have dramatically improved our understanding of the full complexity of MM pathobiology. Eventual relapse to frontline therapies still vexes MM management efforts. Currently, numerous promising compounds, molecular antibodies and immunotherapies are emerging from pre-clinical and clinical evaluation to

broaden the therapeutic armamentarium available to clinicians. Despite the continued accumulation of these new therapies, it is important to heed the lessons learned from decades of studying drug resistance mechanisms in MM: MM's endemic heterogeneous landscape is dynamic and provides numerous avenues by which malignant plasma cells can escape even the most promising therapies. While this seemingly offers little hope to overcome drug resistance in MM, recent studies have demonstrated that with accurate prospective profiling, most tumors can be exposed to harbor targetable weaknesses. Very recently a MM precision medicine trial conducted at Mount Sinai published very encouraging findings that demonstrate the positive results that combined genomic/transcriptomic profiling can yield when subjected to a well-designed analysis pipeline that directs therapy based on knowledge accumulated in the CIViC database (https://civicdb.org) [190].

Adopting precision into routine clinical practice has the potential to radically change the natural history of multiple myeloma. As molecular profiling methods become increasingly affordable and reliable, it is easy to envision a future for disease management that is completely data driven.

Some quantitative technologies discussed above require continued development to increase feasibility and affordability, while others presently demonstrate mature translational feasibility in accurately profiling MM for treatment-specific biomarkers. This begs the question: why are these technologies not being rapidly integrated with the compendium of putative therapeutic biomarkers to offer patients the best opportunity for complete response?

The future of clinical trial design in MM is a subject of ongoing debate where new biomarker-directed approaches (e.g., umbrella trials) are being explored. An ethical conundrum exists between the need for randomized control arms in biomarker directed trials (providing a statistical evaluation of efficacy) and the understandable objection patients enrolled in such trials have towards being randomly denied targeted therapies. Many fairly insist that efficacy of new therapies can only be statistically determined through trial designs that contain randomized control arms rather than relying on historical data [191]. We argue that this approach, which largely focuses on biomarkers for sensitivity, fails to maximize the benefit to enrolled patients. We suggest that such trials should be designed such that patients who also harbor biomarkers for resistance to standard of care therapies should be prioritized for experimental trial arms.

Each patient deserves the most effective, data-driven therapeutic regimen tailored to their individual MM case. Successfully addressing this clear and obvious need will require bold shifts in the current paradigm of clinical trial design and routine disease management. Finally, we bluntly query: at what threshold would precision medicine strategies become reliable enough that it will become irresponsible not to incorporate prospective profiling methods into routine clinical practice to give each patient the most informed treatment plan possible?

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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