bjh commentary

Good news for acute myeloid leukaemia patients from the stroll niche?

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For a long time, acute myeloid leukaemia (AML) has been considered exclusively driven by critical mutations in haematopoietic stem cells (HSCs) (Döhner *et al.*, 2015) but such an HSC-centred approach failed to fully disclose the mechanisms of leukaemia initiation and progression. Recently, the involvement of the bone marrow (BM) microenvironment and stromal cells, including mesenchymal stromal cells (MSCs), has gained increasing interest, questioning the evidence that AML derives exclusively from cell-intrinsic defects (Korn & Méndez-Ferrer, 2017; Tabe & Konopleva, 2017). In particular, MSCs, originally recognized as pivotal providers of the HSC niche (Morrison & Scadden, 2014), have revealed other unexpected and less welcome talents. The alterations, primarily occurring in MSCs, could directly cause HSC dysfunction, favouring leukaemia in mice and patients (Walkley *et al.*, 2007; Santamaría *et al.*, 2012; Zambetti *et al.*, 2016). Moreover, MSCs supply AML cells pro-survival signals contributing to create a malignant cell-protective niche, at the expense of normal HSCs (Korn & Méndez-Ferrer, 2017; Tabe & Konopleva, 2017). Thus, a bi-directional and complex interaction exists among malignant cells and the BM microenvironment, and specifically MSCs, contributing to AML onset and progression. However, the mechanisms underlying this cross-talk are far from being fully elucidated.

Exploring the role of MSC in supporting leukaemia cell survival and investigating genes involved in adipogenic differentiation, the study by Yajing Jiang and collaborators identifies *aldo-keto reductase (AKR)1C1* as a significantly up-regulated gene in MSCs isolated from AML patients (AML-MSCs).

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AKR1C1 belongs to the AKR superfamily, in particular to the AKR1C subfamily (Penning *et al.*, 2000). The AKRs are cytosolic enzymes which reduce, in a NADP(H)-dependent manner, a wide range of substrates, including aldehydes and ketones, to their corresponding primary and secondary alcohols. In particular, AKR1C1 inactivates progesterone, which in turn inhibits glucocorticoid-induced lipogenesis (Penning *et al.*, 2000). Thus, in adipose tissue, AKR1C1 activation results in pre-adipocyte differentiation and fat accumulation (Pedersen *et al.*, 2003; Tchernof & Richard, 2015). Accelerated BM adipogenesis has been associated with ageing and several chronic conditions (Rosen *et al.*, 2009). Moreover, AML-MSCs show a more efficient adipogenesis and a delayed osteogenesis (Chen *et al.*, 2014; Geyh *et al.*, 2016). A marked differentiation capacity in the adipogenic direction has a strong impact in the haematopoietic niche. Adipogenesis negatively influences haematopoietic activity (Naveiras *et al.*, 2009; Kamata *et al.*, 2014), while osteogenesis has a positive effect (Calvi *et al.*, 2003). Thus, increased adipogenesis in the leukaemic BM microenvironment could account for normal HSC exhaustion and award a competitive advantage to leukaemia cells allowing them to occupy quiescent BM. The authors demonstrate that knockdown of *AKR1C1* in MSCs inhibits adipogenesis and stimulates osteogenesis. Reasoning that a modulation in differentiation ability may affect MSC stromal functions, the authors show that AML cells co-cultured with *AKR1C1 knocked-down* MSCs display significantly lower proliferation rates, and accordingly, increased apoptosis and reduced colony-forming abilities, compared to AML cells cultured with control MSCs. The expression of recombinant AKR1C1 rescues the altered differentiation properties and the pro-leukaemia stromal functions of AML-MSCs.

This work also demonstrates that AKR1C1 modulates a further stromal function of MSCs, i.e. cytokine production. It is well known that MSCs produce a large variety of cytokines favouring HSC quiescence or self-renewal (Dazzi *et al.*, 2006) and, at the same time, potentially acting as pro-survival factors for leukaemic cells (Pan *et al.*, 2014; Karjalainen *et al.*, 2017). The secretome of MSCs is altered in the leukaemic BM. Leukaemic MSCs show an increased expression of pro-inflammatory molecules and a reduced expression of factors essential for

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HSC maintenance and differentiation (Chen *et al.*, 2016; Zambetti *et al.*, 2016; Diaz de la Guardia *et al.*, 2017; von der Heide *et al.*, 2017). Yajing Jiang and collaborators demonstrate that AKR1C1 knockdown modifies the transcriptional and secretory cytokine profile of AML-MSCs, especially reducing the production of Monocyte Chemoattractant Protein (MCP)-1, Interleukin (IL)-6, IL-8 and granulocyte-colony stimulating factor (G-CSF). The mechanism is unclear, but it could be hypothesized that, since AKRs reduce a wide variety of lipophilic substrates, they could therewith modulate ligand access to nuclear receptors affecting the transcription of several genes (Penning & Drury, 2007), including those involved in cytokine pathways. The authors show that stimulation with cytokines, especially IL-6, is able to restore the pro-leukaemia stromal functions of *AKR1C1 knocked-down* MSCs. This is consistent with the pivotal role of IL-6 as modulator of the BM microenvironment and as pro-survival factor for AML cells (Golay *et al.*, 2007; Fisher *et al.*, 2014). The authors also investigate the downstream pathway of IL-6 and they found that Signal transducer and activator of transcription (STAT)-3 and extracellular signal–regulated kinase (ERK)1/2 activation is reduced in AML cells co-cultured with *AKR1C1 knocked-down* MSCs and increased following pre-treatment with recombinant ARK1C1. Thus, they conclude that ARK1C1 favours AML cell survival by stimulating the MSC secretion of cytokines, mainly IL-6. In turn, cytokine production induces a STAT3/ERK-dependent pro-survival pathway in AML cells.

Up-regulation of the *AKR1C1* gene in AML-MSCs is in agreement with similar observations in other frameworks. Indeed, AKR enzymes are ubiquitously expressed in normal tissues and overexpressed in diverse tumour cells (Chen *et al.*, 2005; Hung *et al.*, 2006; Rizner *et al.*, 2006; Byrns *et al.*, 2010). Recent evidence indicates that AKR aberrant expression correlates with the response to chemotherapy in solid tumours and leukaemia (Veitch *et al.*, 2009; Matsunaga *et al.*, 2016; Bortolozzi *et al.*, 2018). In this work, the authors outline that analysis of data in the Cancer Genome Atlas database (TGCA) indicates a worse overall survival in the *AKR1C1*-high expressing group of AML patients. To note, over-expression of *AKR1C1* in AML cells did not significantly affect their proliferation, apoptotic rate and colony-forming ability, suggesting that the AKR1C1-dependent pro-leukaemia effect requires stromal attendance. A possible involvement of *AKR1C1* overexpression in modulating AML cell survival/resistance to therapy is not surprising. AKR enzymes play an important role in the detoxification of a large number of pharmaceuticals, drugs and environmental pollutants (Barski *et al.*, 2008). Thus, AKRs are the predominant enzymes protecting cells against damage, but they are also decisive in modulating drug action and toxicity. Several pharmacological compounds are potential substrates (or regulators) of AKRs. For some drugs, modification by AKRs is necessary to active them. For others, including anticancer drugs (e.g. daunorubicin, doxorubicin), reduction by AKRs represents the deactivation step (Barski *et al.*, 2008). In the latter case, AKR activity could diminish drug anti-tumour efficacy. Thus, the expression state of drug-metabolizing enzymes could potentially contribute to drug resistance and hence it might be taken into account in the choice of therapy.

In summary, the study by Yajing Jiang and collaborators sheds light on four different aspects emerging as pivotal in MSC-driven pro-leukaemia mechanisms:

1. Alterations in the MSC gene-expression programme potentially affecting MSC functions.
2. The defective balance between osteogenic and adipogenic MSC differentiation potential, eventually resulting in BM failure and awarding a competitive advantage to leukaemia cells.
3. The MSC aberrant cytokine production with a different impact on HSC and/or leukaemia cell supporting ability.
4. The MSC-dependent mechanism(s) of resistance to therapy.

Although many gaps remain to be filled in the overall picture, it is becoming increasingly clear that considering the BM microenvironment, besides the malignant cells, is crucial for reaching a comprehensive understanding of haematological diseases. Current AML treatments are mainly focused on the targetting of leukaemia cells, and often neglect the hold of the BM microenvironment. An increasing body of evidence indicates that MSC alterations in the leukaemic microenvironment contribute to creating an AML-permissive/self-reinforcing niche favourable to escaping therapy and immune response. Thus, as with other malignancies, the design of therapies that, besides targetting the root, takes into account the fertile soil where the disease grows, could translate into a better and deeper control of the disease.

Author Contributions

MC drafted the manuscript. AC participated to draft and revised the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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