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Commentary

Alliance of galectin-3 and CD74 biochemical networks as a crucial component of survival machinery operated by human acute myeloid leukaemia cells

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Acute myeloid leukaemia (AML) is a severe systemic malignancy originated from self-renewing transformed immature myeloid precursors. AML can often be a fatal disease since transformed cells operate highly effective machinery which allows them to protect themselves against induction of programmed cells death and also to suppress anti-cancer activity of natural killer (NK) and cytotoxic T cells (CTCs) thus evading immune attack [4, 6]. These biochemical networks act as a "multilayer protection cover" for AML cells since even if they are attacked by the immune cells, their killing becomes problematic due to effectiveness of anti-apoptotic machinery. Therefore, it is crucially important to understand the mechanisms underlying functional activity of anti-apoptotic biochemical networks operated by AML cells in order to select optimal targets and design new drugs for successful and efficient therapy.

In the study published in this issue of *EBioMedicine*, Ruvolo and colleagues have demonstrated that two biochemical cell survival pathways controlled by galectin-3 (a beta-galactoside-binding protein) and cluster of differentiation (CD) 74 (a signalling receptor and a chaperone for major histocompatibility complex type II proteins which are involved in antigen presentation) are cross-linked in a biochemical protein network, which is associated with poor survival of AML patients [7]. Importantly, this invaluable clinical study was performed using samples obtained from a large number of AML patients (511 in total) with newly diagnosed disease when malignant cells normally display high pro-survival and immune evasion activities. The study reports that galectin-3 expression is prognostic for poor survival rate of AML patients. Survival rate of AML patients with galectin-3 positive malignant cells was even lower when CD74-dependent signalling networks (in particular, the one involving transmembrane receptor known as CD44) were active. Intriguingly, the study reported galectin-3 to act as a negative regulator of the protein phosphatase 2A (PP2A), the enzyme involved in deactivation of several intracellular signalling cascades (see below). It was shown that galectin-3 affects regulatory (B) subunit of

this enzyme (the enzyme has three subunits – structural (A), regulatory (B) and catalytic (C), [7]).

This work is of great value for both basic and clinical AML research since it is not just a report of cross-links between biochemical networks but also a solid clinical verification of the evidence obtained in basic *in vitro*, *ex vivo* and *in vivo* studies, which can now be put together in order to identify the best targets for complex anti-AML therapy.

AML cells operate several pathways which allow them to disable cytotoxic lymphoid cells (NK and CTCs; summarised in the Fig. 1). This includes implication of CD86-CTLA4 (cytotoxic T-lymphocyte-associated protein 4) as well as ligands of programmed cell death protein (PD-L)-PD1 pathways [10]. Furthermore, AML cells operate Tim-3 (T-cell immunoglobulin and mucin-domain containing protein 3)-galectin-9 (another member of galectin family of proteins, [4]) secretory pathway which impairs anti-AML activities of both NK cells and CTCs. However, if AML cell is attacked by cytotoxic lymphoid cells or subjected to action of endogenous (e. g. pro-apoptotic cytokines) or exogenous (e. g. drugs) inducers of apoptosis, it manages to survive with the help of galectin-3 and CD74/CD44 signalling networks which appear to be connected [7].

From recent reports, we know that galectin-3 is capable to protect mitochondria against defunctionalisation mainly *via* direct interaction with proteins from Bcl (B cell lymphoma) -2 family including anti-apoptotic Bcl-2 and pro-apoptotic Bax proteins [5,6,9]. As a result of these interactions, Bcl-2 protects mitochondria and Bax loses its capability to cause mitochondrial dysfunction resulting in cytochrome *c* release followed by caspase-3/caspase cascade activation and apoptosis (Fig. 1). Importantly, galectin-3 has NWGR (Asn-Trp-Gly-Arg) motif specific to Bcl-2 family proteins which is necessary for homo- or heterodimerisation of these proteins and thus is capable of interacting with them [5,9]. Other galectin family members (for example galectin-9), despite their ability to interact with defunctionalised mitochondria in malignant cells [8], do not have this motif and thus do not display such an activity.

CD74 and CD44 receptor alliance, activated by the ligand called macrophage migration inhibitory factor (MIF), is capable of activating Ras/ERK (extracellular signal-regulating kinase) and phosphatidylinositol-3 kinase (PI-3 K)/Akt pathways [1, 7]. Also, active CD74 can undergo intermembrane proteolytic cleavage and activate its intracellular domain which displays functional activity. All these pathways activate
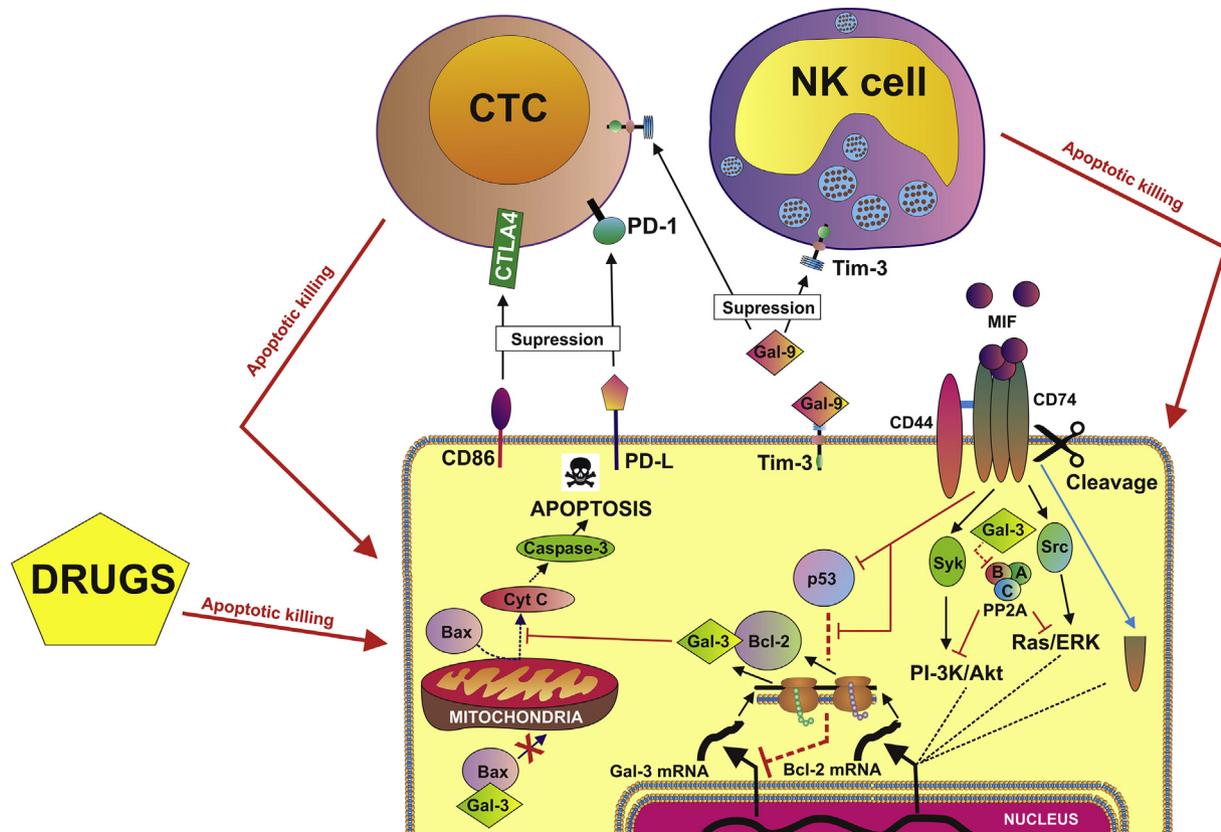
Fig. 1. Anti-apoptotic and immune evasion machineries operated by human AML cells. Galectins 3 and 9 are abbreviated as Gal-3 or Gal-9 respectively.

transcription factors thus leading to expression of various genes, one of which is Bcl-2 ([1], Fig. 1).

Tumour suppressor protein p53 was reported to block expression of galectin-3 by repressing transcription of its gene [2]. However, CD74/CD44 activated by MIF, cause suppression of p53 activity [3] thus making galectin-3 expression possible (Fig. 1). On the other hand, PP2A, the enzyme mentioned above, targets crucial components of PI-3 K/Akt and Ras/ERK pathways leading to loss of their activities. Ruvolo and Co-Authors have shown that galectin-3 downregulates PP2A activity and thus prevents de-activation of AML cell survival pathways ([7], Fig. 1).

So, in addition to its novelty, the work of Ruvolo and colleagues provides excellent clinical verification of recently acquired basic knowledge. Furthermore, the study clearly demonstrates that galectin-3 and CD74 are promising targets for anti-AML therapy.

Disclosure

The authors declared no conflicts of interest.

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