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Progress in BCL2 inhibition for patients with chronic lymphocytic leukemia

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ABSTRACT

The prosurvival protein BCL2 is uniformly expressed in chronic lymphocytic leukemia (CLL), and enables leukemia cell survival in the face of cytotoxic treatment and increasing genomic, metabolic, and oxidative stresses. The therapeutic potential of BCL2 inhibition was first observed in the clinic following BCL2 antisense therapy. Subsequently, a number of small molecule inhibitors were developed to mimic the function of the pro-apoptotic BH3-only proteins (BH3-mimetics). These molecules are now in late-phase clinical trials and demonstrate potent activity, including the occurrence of acute tumor lysis syndrome in subjects with multiply relapsed, chemorefractory CLL. In this review, we discuss the history and summarize current knowledge regarding BCL2 inhibition as therapy of CLL.

1. BCL2 family proteins and their role in CLL

The gene partner juxtapositioned to the IgH locus in the t(14;18)(q32;q21) translocation was identified as BCL2 (named for B-cell lymphoma 2) in 1984, a gene of unknown function at the time [1]. In 1988, Vaux and colleagues made the seminal observation that transfection of BCL2 into interleukin-3 (IL-3)–dependent cell lines allowed the cells to survive in the absence of IL-3, but these cells persisted in a G_0 state and did not proliferate [2]. What we know now is that the BCL2 family of proteins are key regulatory components of the intrinsic (mitochondrial) apoptosis pathway [3], an important physiological process that is often hijacked and disabled by cancer to enable cellular survival in the face of high levels of genomic, metabolic and oxidative stresses [4].

There have been several excellent recent reviews of the intrinsic apoptosis pathway (see [3] as a recent example) and a simplified schematic is presented in Fig. 1. BCL2 family proteins can be divided into three functional groups: (1) “executioner” proteins (BAX and BAK) which are normally restrained by the (2) “anti-apoptotic” proteins (BCL2, BCL_{XL}, BCL_W, MCL-1 and A1); in response to cellular triggers to commit suicide, the (3) “BH3-only” proteins (BIM, PUMA, BAD and NOXA) bind the anti-apoptotic proteins, thus releasing BAX and BAK and initiating the cascade that leads to apoptosis [3,5]. Some BH3-only proteins may also activate BAX and BAK directly [6]. The cellular events that activate the BH3-only proteins are not fully understood, but different members of the BH3-only family respond to different triggers. For example, BIM can be activated by endoplasmic reticulum stress [7], whereas PUMA and NOXA respond to activation of the P53 pathway by, for example, DNA damage from cytotoxic chemotherapy [8–10]. The BH3-only family proteins exert their biological effect through their BH3 ligand domain, which inserts into binding grooves on the anti-apoptotic proteins [3,11,12]. There is selectivity in this binding due to minor variations in the BH3-binding cleft of prosurvival proteins: for example, whereas BIM and PUMA bind all members of the anti-apoptotic family, BAD binds preferentially to BCL2, BCL_{XL}, and BCL_W, whereas NOXA binds preferentially to MCL-1 (Fig. 2) [13]. This variation also enables selectivity in binding by small molecules. This has proven important in allowing us to design drugs to exploit the anti-cancer potential of BCL2 inhibition, while avoiding “on-target” side effects such as BCL_{XL} inhibition related thrombocytopenia [14].

BCL2 and the related anti-apoptotic proteins are attractive therapeutic targets in chronic lymphocytic leukemia (CLL). BCL2 is uniformly overexpressed in CLL, often at levels higher than those seen in follicular lymphoma with translocation (14;18) [15,16]. The mechanisms of this BCL2 over-expression are diverse and include the deletion of mir-15 and mir-16 (a consequence of the common 13q14 deletion [17]), which results in increased expression of the normally suppressed mir-15 and -16 targets BCL2 and MCL-1 [18]. Increased resistance to cell death in vivo is a hallmark of CLL, where tumor cells typically accumulate slowly over a period of many years, often in the face of increasing genomic aberrations

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