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PIM activity in tumours: A key node of therapy resistance

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ABSTRACT

The PIM kinases are proto-oncogenes which have been shown to facilitate cell survival and proliferation to drive malignancy and resistance post-therapy. They are able to suppress cell death signals, sustain PI3K/AKT/mTORC1 pathway activity and regulate the MYC oncogenic program. Recent work has revealed PIM kinase essentiality for advanced tumour maintenance and described tumour sensitivity to small molecule inhibitors targeting PIM kinase in multiple malignancies.

1. Introduction

The PIM kinases (PIMs) offer promising potential as therapeutic targets, they are potent oncogenic drivers in hematologic malignancy and are considered to be essential in the progression of other tumours, namely prostate and breast adenocarcinoma (Nawijn et al., 2011). Their name was derived from the discovery that the *PIM1* locus (6p21.2) was the most frequent insertion site of the Moloney murine leukemia virus. These early experiments demonstrated that overexpression of this locus lead to lymphoma in mice (Cuypers et al., 1984). Accordingly, subsequent studies showed that transgenic mice (Eμ-Pim1) which overexpress *PIM1* as driven by the immunoglobulin heavy chain (IgH) enhancer also develop lethal T-cell lymphoma (Breuer et al., 1989; van Lohuizen et al., 1989). Evidence of synergy with the MYC oncogene in disease acceleration was seen in these early experiments (Breuer et al., 1991), a relationship which is now well established and believed to be a key interaction of PIM signalling in tumours. The other members of this family, *PIM2* (Xp11.23) and *PIM3* (22q13) are paralogs of *PIM1* and share more than 60 percent sequence homology. They are all calmodulin-dependent protein kinases (CAMK) and have the capacity to initiate and drive lymphomagenesis (Keane et al., 2015). Notably, PIM kinases lack a regulatory domain and are constitutively active (Qian et al., 2005), therefore expression of PIM directly correlates with activity. PIM1 and PIM2 also have distinct isoform variants generated by alternative initiation codon usage and giving rise to 44 and 34 kDa isoforms (Keane et al., 2015). The PIMs function as serine/threonine kinases (Hoover et al., 1991; Padma and Nagarajan, 1991; Selten et al., 1986), which catalyse the phosphorylation of many different cellular growth and survival signalling substrates which are key intermediate regulatory nodes of the PI3K/AKT/mTORC1 pathway and also transcription factors involved in cell cycle progression and cell death signalling (see Fig. 1).

2. The PIM kinase network in cancer

PIM kinases (PIMs) are widely overexpressed in hematologic malignancy and are known to be significant drivers of disease

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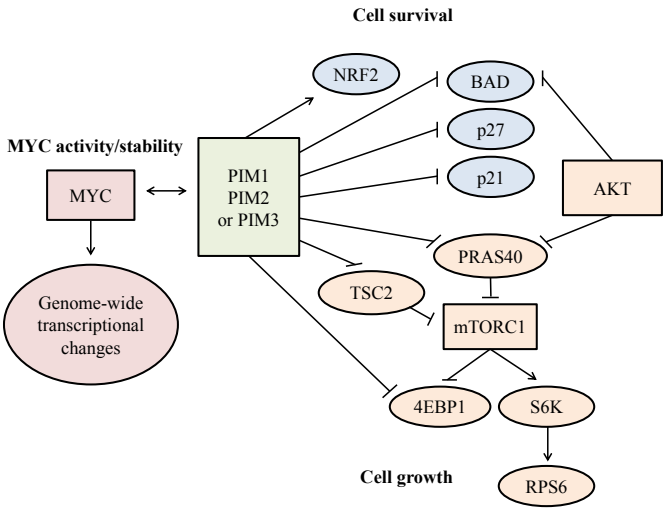

Fig. 1. Key PIM kinase substrates.

PIM kinases phosphorylate and attenuate pro-apoptotic signals through NRF2, BAD, p27 and p21. Equally, PIM kinases function to regulate growth signalling through the PI3K/AKT/mTORC1 pathway by sustaining activity of mTORC1 and downstream substrate activity, namely by inhibiting TSC2, PRAS40 and 4EBP1. Finally, PIM kinases regulate MYC protein stability and MYC-dependent transcription, positively regulating the MYC transcriptional program.

(Nawijn et al., 2011). *PIM1* mRNA is highly abundant in acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) and diffuse large B cell lymphoma (DLBCL) whereas *PIM2* mRNA is mainly overexpressed in multiple myeloma (MM) and *PIM3* overexpression is observed in ALL (Garcia et al., 2014). However, expression of PIM kinases often correlates with decreased overall survival and is associated with therapy resistance in a range of solid tumours as well (Nawijn et al., 2011). PIM1 is overexpressed in both early non-malignant (Cibull et al., 2006), and high-grade prostate cancer (Dhanasekaran et al., 2001; Wang et al., 2010) as well as in triple negative breast cancer (Braso-Maristany et al., 2016). Recently, the overexpression of PIM kinases has also been reported to drive disease progression in pancreatic ductal carcinoma (Li et al., 2006; Xu et al., 2016), hepatocellular carcinoma (Wu et al., 2010) and glioblastoma multiforme (Herzog et al., 2015). PIM kinases are thought to have key influence in tumour maintenance post therapy. For example, experimental overexpression of PIM1 enhances the proliferation of prostate and breast tumour cells post chemotherapy (Chen et al., 2005) and in the hormone refractory setting (Braso-Maristany et al., 2016; Ha et al., 2013). Thus, PIM kinases are not only potential therapeutic candidates in haematological malignancy, but also in multiple solid tumour types.

3. Control of cell cycle and cell survival

PIM kinases are currently thought to govern progression through the cell cycle, sustain cell growth and proliferation as well as regulate cell death in response to nucleolar stress. PIM localisation within the cell has been reported as both nuclear (Bhattacharya et al., 2002) and cytoplasmic (Lilly et al., 1999) mediating a multitude of changes to the cell signalling program. In the nucleus, PIM1 is shown to associate with nuclear mitotic apparatus (NuMA), promoting its complexation, a requirement for mitosis as well as phosphorylation of histone H3, which is necessary for MYC-dependent transcriptional activity (Bhattacharya et al., 2002; Zippo et al., 2007). The deletion of PIM1 does not affect viability in untransformed prostate cells (Roh et al., 2003) and mice which harbour the deletion of all PIM genes are viable and fertile (Mikkers et al., 2002, 2004) exemplifying the redundancy in the PIM network and the potential for PIM inhibitors as cancer therapeutics with favourable tolerability.

PIM is robustly upregulated in the tumour in response to genotoxic stress which can be triggered by the use of chemotherapy and is involved in survival beyond these events. Zemskova and colleagues showed that PIM1 abundance is increased in prostate cancer cells treated with the chemotherapeutic agent, docetaxel (Zemskova et al., 2008). Docetaxel is shown to induce PIM1 expression in a DNA damage-dependent manner and PIM activity is an important factor in docetaxel resistance (Zemskova et al., 2008). Here, prostate cancer cells with intact p53 undergo senescence but not death upon overexpression of PIM (Zemskova et al., 2010). Jin and colleagues have recently corroborated these findings as PIM1 is upregulated during treatment of ovarian cancer cells with chemotherapy, which mediates cell cycle arrest instead of death (Jin et al., 2014). Additionally, it was shown that PIM1 regulates CHEK1 kinase activity to arrest cells in G2/M phase of the cell cycle in AML upon treatment with etoposide. In this context, the silencing of PIM bypasses cell cycle arrest and the cell dies (Yuan et al., 2014). Conversely, single agent treatment of AML cells with pan-PIM inhibitor AZD1208 results in the phosphorylation and activation of CHEK2, inducing cell cycle arrest in cells with low levels of apoptosis observed (Chen et al., 2016). Chen and colleagues further demonstrated that upregulated PIM1 modulates sensitivity to chemotherapy by directly phosphorylating BCL2 associated death promotor (BAD) at serine 112 (Chen et al., 2009a). This is thought to be central to PIM kinase pro-survival function in the tumour (Lilly et al., 1999; Yan et al., 2003), the consequence of BAD phosphorylation raises the threshold required for the cell to initiate the cell death cascade. Musiani and colleagues showed that platinum-based chemotherapy is a strong inducer of all PIM paralogs in ovarian tumour cells, and that inhibitory phosphorylation