ligase activity, kinase-bound phosphorylated c-CBL rapidly undergoes degradation,[26] by which positive signaling should be terminated. Thus, once linker/RING finger mutations abolish the E3 ligase activity of c-CBL, the consequence would be prolonged signaling due not only to loss of negative regulation of tyrosine kinase, but also to enhanced positive regulatory functions, which should appear as gain-of-function (Fig. 4).

In contrast to the CBL-b inhibition model, the uni-laterality of c-CBL mutations could be more easily explained, because c-CBL and CBL-b have distinct biological functions, as clearly shown by the phenotypes of *c-CBL*$^{-/-}$ and *CBL-b*$^{-/-}$ mice.[22,23,49,50] For example, CBL-b lacks one of the major phosphorylated tyrosines, Y731, that provides a docking site for the p85 subunit of PI3 kinase. Although the exact molecular basis for the distinct functions between both CBL proteins remains to be elucidated, c-CBL-specific positive regulatory function in immature hematopoietic progenitors may be important for the pathogenesis of myeloid neoplasms.

Conclusion

Allelic conversion leading to aUPD is an important genetic mechanism of clonal evolution in the pathogenesis of MPN, and associated not only with loss-of-function of tumor suppressor genes, but also with gain-of-function mutations of proto-oncogenes. Homozygous *c-CBL* mutations that characterize a subset of MDS/MPD carrying 11q-aUPD, represent a unique example of gain-of-function mutations of tumor suppressor/proto-oncogene. These linker/RING finger mutations convert c-CBL, which otherwise act as a tumor suppressor, to a gain-of-function oncogenic protein. Although its exact molecular mechanism is still unknown, the gain-of-function of oncogenic c-CBL mutants seems to be related to disintegration of negative and positive regulatory machineries of normal c-CBL protein. Detailed analysis of the oncogenic mechanisms of c-CBL mutants is warranted, which should shed light on a novel aspect of physiological function of c-CBL. Considering their expression and functions in a broad spectrum of tissues, *CBL* family genes may be mutated in other human cancers.

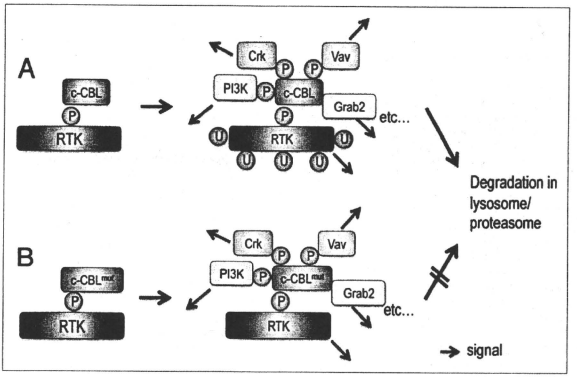

Figure 4. Positive regulation of signal transduction by c-CBL. (A) Having E3 ubiquitin ligase activity for negative regulation of signaling, c-CBL also works as an adaptor protein for multiple signal transduction molecules. When bound to phosphorylated tyrosine kinases, c-CBL is rapidly phosphorylated at multiple tyrosine residues, which in turn provide binding sites for a number of signal transduction molecules. Several lines of evidence suggest that binding to these molecules plays important roles in positive regulation of signal transduction (red arrows). Normally, phosphorylated c-CBL undergoes degradation, which is mediated by its E3 ubiquitin ligase activity. Thus, degradation of mutated c-CBL could be retarded, leading to prolonged transmission of positive signals (B).

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