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REVIEW

Oncogenic re-wiring of cellular signaling pathways

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Signaling pathways in mammalian cells are assembled and regulated by a finely controlled network of protein–protein and protein–phospholipid interactions, mediated by dedicated signaling domains and their cognate binding motifs. The domain-based modular architecture of signaling proteins may have facilitated the evolution of complex biological systems, and can be exploited experimentally to generate synthetic signaling pathways and artificial mechanisms of autoregulation. Pathogenic proteins, such as those encoded by bacteria and viruses, frequently form ectopic signaling complexes to respecify cellular behavior. In a similar fashion, proteins expressed as a consequence of oncogenic fusions, mutations or amplifications can elicit ectopic protein–protein interactions that re-wire signaling pathways, in a fashion that promotes malignancy. Compounds that directly or indirectly reverse these aberrant interactions offer new possibilities for therapy in cancer.
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Molecular architecture of signaling pathways

Cell surface receptors, such as receptor tyrosine kinases (RTK), transmit signals through a series of regulated molecular interactions, mediated by dedicated non-catalytic domains (Hunter, 2000; Pawson and Nash, 2003). In the case of RTKs, binding of the appropriate extracellular growth factor leads to a reorganization of receptor chains, usually by dimerization, and this results in the intermolecular autophosphorylation of cytoplasmic tyrosine sites that perform two related functions (Heldin, 1995). Phosphorylation of a tyrosine residue in the activation segment of the kinase domain can cause a structural change that enhances kinase activity, by promoting a catalytically competent conformation at the active site (Hubbard, 1997; Hubbard and Till, 2000). However, the majority of autophosphorylation sites are located in motifs that bind the Src homology 2 (SH2) domains of cytoplasmic effectors and regulators, which in turn control intracellular signaling pathways, as well as regulating the activity and internalization of the receptor (Anderson *et al*., 1990; Pawson and Nash, 2000; Hu *et al*., 2003; Haglund and Dikic, 2005).

Bioinformatic analysis indicates that the human genome encodes 120 SH2 domains, contained within 110 proteins, which in aggregate are likely to mediate the cellular responses to phosphotyrosine signaling (Liu *et al*., 2006). These polypeptides have a range of distinct biochemical functions, involving phospholipid metabolism, the cycling of Ras-like GTPases, protein phosphorylation and dephosphorylation, organization of the cytoskeleton, gene expression and ubiquitination. A number of such SH2-containing proteins possess intrinsic catalytic domains, whereas others are composed exclusively of interaction domains, and act as adaptors or scaffolds to physically couple activated receptors to specific downstream targets. A common feature of these proteins, and indeed of most gene products in RTK signaling pathways, is their modular architecture, in the sense that they contain multiple folded domains, with either interaction or catalytic functions. These domains are often separated by unstructured regions, which contain short peptide motifs that are recognized by catalytic domains (for example a phosphorylation site), or interaction domains (such as proline-rich motifs that bind SH3 domains) (Zarrinpar *et al*., 2003), or both, as in the case of a tyrosine-containing motif that is first phosphorylated by a tyrosine kinase, and consequently recruits an SH2 domain.

Interaction domains assemble and regulate signaling pathways

This rather simple arrangement can underlie more complex regulation, for example, through the intramolecular association of a peptide motif with a cognate interaction domain to yield an autoinhibited state, as in the case the Src cytoplasmic tyrosine kinase. In the inactive Src conformation, the association of an SH2 domain with the phosphorylated tail, and of the SH3 domain with the SH2-kinase linker region, restricts the activity of the kinase domain (Figure 1a) (Sicheri *et al*., 1997; Xu *et al*., 1997). This inhibition is reversed by breaking these intramolecular interactions, for example by dephosphorylation of the tail (or its deletion in the

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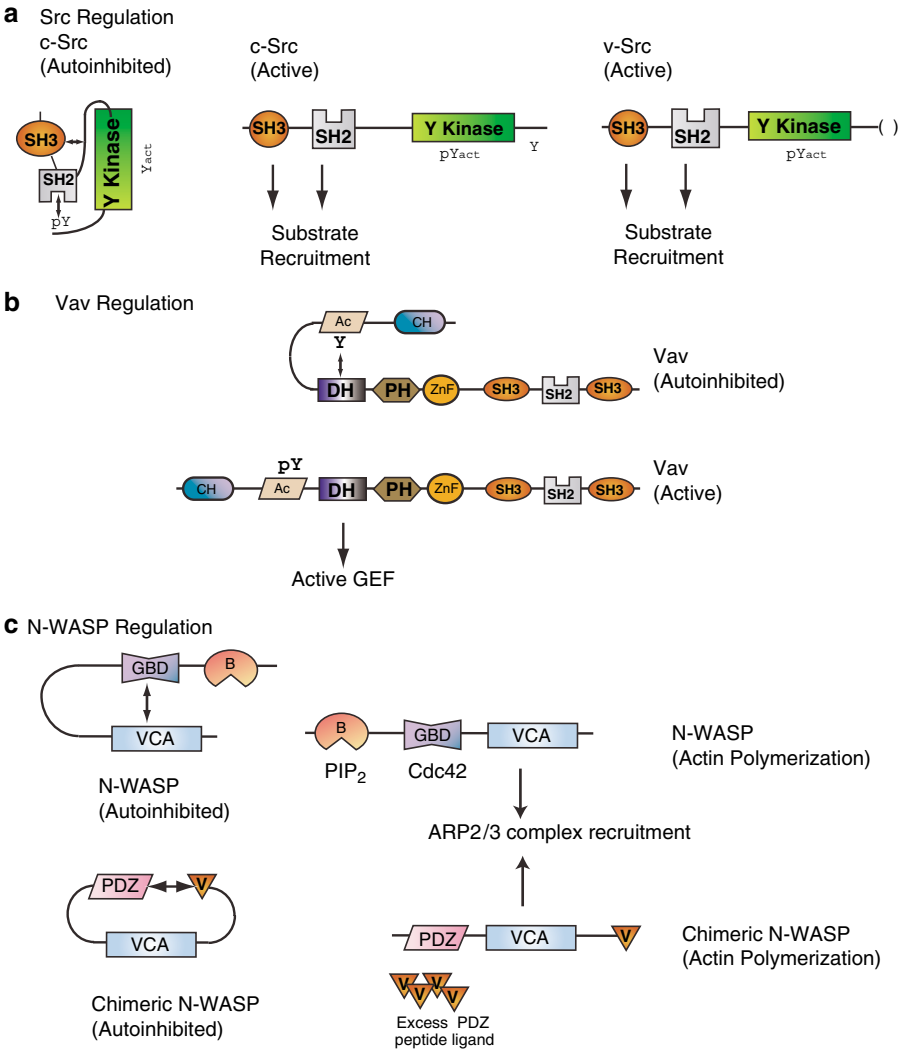

Figure 1 Protein domains and binding motifs mediate autoinhibitory interactions. The modular domain structures and the intramolecular interactions that regulate signaling of the cytoplasmic tyrosine kinase Src (**a**), the GEF Vav (**b**) and the scaffolding protein N-WASP (**c**) are shown. A virally encoded oncogenic version of Src lacking the C-terminal phosphoregulatory site is shown. In addition, a chimeric version of N-WASP in which the natural autoinhibitory interactions are artificially replaced by a PDZ domain and PDZ-binding motif is also depicted. Abbreviations: AC, *Ac*idic motif; ARP, *A*ctin *R*elated *P*rotein; B, *B*asic region; CH, *C*alponin *H*omology domain; DH, *D*bl *H*omology domain; GBD, *G*TPase *B*inding *D*omain; N-WASP, *N*euronal *W*iskott–*A*ldrich *S*yndrome *P*rotein; PDZ, *P*SD95, *D*lg, *Z*O-1 homology domain; PH, *P*leckstrin *H*omology domain; SH, *S*rc *H*omology domain; a V in a triangle represents a PDZ domain-binding motif; VCA, *V*erprolin homology, *C*ofilin homology, *A*cidic domain, pYact represents kinase domain activation loop phosphorylation and kinase activity; ZnF, *Zinc F*inger. Please see the text for more details on the regulatory properties of each of the illustrated multidomain proteins.

case of oncogenic v-Src), thereby liberating both the SH2 and SH3 interaction domains to engage exogenous ligands, and removing the restraint on kinase activity (Brown and Cooper, 1996). In a somewhat similar fashion, a short acidic motif (Ac) in the Rho/Rac guanine nucleotide exchange factor (GEF), Vav, folds against the adjacent catalytic Dbl homology (DH) domain to block GEF activity (Figure 1b) (Aghazadeh *et al*., 2000). This inhibition is removed by phosphorylation of a tyrosine in the inhibitory motif by Src family kinases, which displaces the Ac motif and thereby stimulates GEF activity. Single particle electron microscopy (EM) of inactive Vav suggests that a Calponin homology (CH) domain, located N-terminal to the Ac–DH region, may stabilize the autoinhibited conformation through multiple interactions with the Ac motif, the DH domain and a more C-terminal zinc-finger domain (Llorca *et al*., 2005). EM analysis also suggests that tyrosine phosphorylation induces a major reorganization of the Ac, CH and DH domains, exposing the DH domain for interactions with a Rho/Rac GTPase. Consistent with these observations, deletion of the N-terminal inhibitory region stimulates Vav transforming activity (Bustelo, 2000). Taken together, data of this sort suggest that the combinatorial use of simple domain–motif interactions can provide

signaling proteins with rather sophisticated regulatory properties.

A consequence of the modular properties of signaling proteins is that pathways downstream of RTKs can be formed through a series of molecular interactions, dependent on specific modifications. As an example, phosphorylation of RTKs on YXXM motifs recruits the SH2 domains of the p85 adaptor subunit of phosphatidylinositol (PI) 3′-kinase, which through its p110α catalytic subunit converts $PI(4,5)P_2$ to $PI(3,4,5)P_3$, creating docking sites at the plasma membrane for the Pleckstrin homology domains of the serine/threonine kinases PKB/Akt and its activator phosphoinositide-dependent kinase 1 (Engelman *et al*., 2006). PKB phosphorylates multiple substrates, and can influence their activity by altering phosphoserine/threonine-dependent protein–protein interactions, for example by inducing the binding of 14-3-3 proteins to apoptotic regulators such as Bad (an inhibitor of the proapoptotic protein Bcl-X_L from which it is displaced by 14-3-3) or Foxo (a transcription factor that is retained in the cytoplasm when bound to 14-3-3) (Zha *et al*., 1996; Brunet *et al*., 1999). Thus through a series of protein and lipid phosphorylation events, and the consequent formation of binding sites for phosphorylation-dependent interaction domains, an extended network of molecular interactions can be formed, with important consequences for cell growth, survival and metabolism. When viewed in this way, the specificity with which cell surface receptors stimulate intracellular pathways, and the amplitude and duration of pathway activation, depend significantly on the accrued effects of domain-based protein–protein and protein–phospholipid interactions.

Synthetic re-wiring of signal transduction

Approximately 70% of human proteins have one or more recognizable domains, based on sequence analysis, begging the question as to why a domain-based architecture is such a prevalent feature of the proteome. As one possible answer to this conundrum, the modular organization of domains and motifs in cellular proteins may have facilitated the evolution of new signaling pathways and biological functions. In this scheme, the acquisition of a new domain or motif may endow an existing protein with new molecular connections, or modes of regulation, and could thereby provide the cell with a novel means of responding to a signaling cue, or of linking the signal to the core cellular machinery (Bhattacharyya *et al*., 2006). This hypothesis predicts that it should be possible to artificially create a new signaling pathway, or a new mode of regulating a catalytic domain, by linking domains together in combinations that are not normally seen in cells. For example, we have created artificial adaptors that contain the SH2 or phosphotyrosine-binding (PTB) domains of the Grb2 or ShcA adaptors to the death effector domain (DED) of the Fas-associated death domain (FADD) adaptor (Figure 2) (Howard *et al*., 2003). In their native form, ShcA and Grb2 couple tyrosine kinases to signaling pathways involved in cell growth, differentiation and survival (i.e. the Ras-mitogen-activated protein (MAP) kinase/PI 3′-kinase pathways), whereas FADD links receptors such as Fas to caspase-8/10, and thus to apoptotic pathways. We found that the chimeric DED-SH2 or DED-PTB adaptors were complexed with caspases, and were recruited to activated RTKs, such

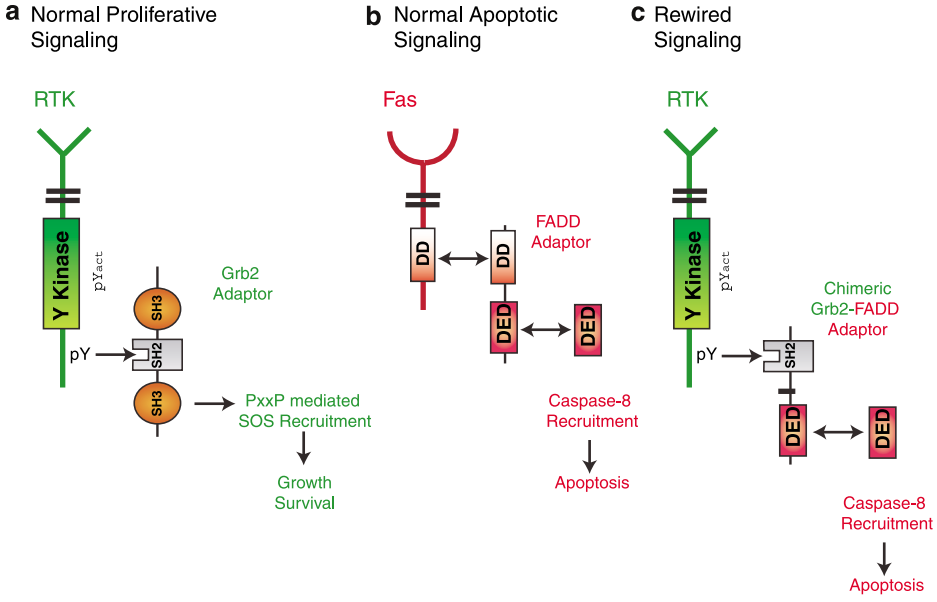

Figure 2 Chimeric adaptor proteins can re-wire cellular signaling pathways. Schematic representations of a growth factor signaling pathway downstream of a cell surface RTK (**a**) and an apoptotic signaling pathway downstream of the Fas cell surface receptor (**b**) are shown. These two opposing pathways were interconnected by generating a chimeric adaptor protein in which the SH2 domain of Grb2 (or the PTB domain of Shc – not shown) was fused to the DED of FADD. The chimeric adaptor protein is capable of re-wiring a proliferative RTK input signal into an apoptotic cell death output signal. Abbreviations: DED, *D*eath *E*ffector *D*omain; DD, *D*eath *D*omain.

as an oncogenic form of *e*rythro*b*lastic leukemia viral oncogene homolog2 (ErbB2). This resulted in caspase activation, likely as a consequence of clustering of the receptor-associated complex, and therefore in cell death. These data indicate that it is possible to re-direct signaling from an RTK to a completely novel pathway, by using an artificial adaptor composed of interaction domains that are never linked in a physiological protein.

The notion that interaction domains and motifs might endow an effector domain with novel regulatory properties has been explored by Lim and co-workers, who have exploited the C-terminal VCA (*V*erprolin homology, *C*ofilin homology, *A*cidic domain) region of the N-WASP (*N*euronal *W*iskott–*A*ldrich *S*yndrome *P*rotein) protein, which engages the Arp2/3 complex to stimulate branching actin polymerization. In the intact N-WASP protein, the VCA region is inhibited through an intramolecular interaction with a GTPase binding domain (GBD), which is relieved when guanosine triphosphate (GTP)-bound Cdc42 associates with the GBD (Figure 1c) (Kim *et al*., 2000). A chimeric protein in which the VCA region of N-WASP was artificially flanked by a PDZ (PSD95, Dlg, ZO-1 homology) domain on one side, and a PDZ-binding motif on the other, was inhibited in its ability to induce actin polymerization, and this inhibition was relieved by an exogenous PDZ-binding peptide (Dueber *et al*., 2003). Furthermore, polypeptides in which the VCA region was surrounded by both PDZ and SH3 domains, and cognate peptide ligands, showed a range of complex gating properties. These findings suggest that interaction domains and motifs can readily confer autoregulatory behavior on associated output domains, even when these elements have not been found together in existing proteins, consistent with the notion that the joining of domains and motifs in new combinations might be one way to enhance biological complexity during the course of evolution.

Pathogenic manipulation of signaling networks

The ability to experimentally manipulate signaling pathways by the creation of artificial, chimeric proteins raises the possibility that pathogenic proteins might also have acquired the capacity to mediate ectopic protein–protein interactions, and thus to re-wire cellular behavior. Indeed, there are many examples of bacterially- and virally encoded proteins that have acquired short motifs that interact with cellular targets, and thereby respecify signaling networks. As an example, the Tir protein of enteropathogenic *Escherichia coli* (EPEC) and the A36R product of vaccinia virus both possess a very similar tyrosine-based motif (YDXV) that is phosphorylated by cellular tyrosine kinases, and consequently recruits the SH2 domain of the Nck adaptor protein, which in turn binds to cytoskeletal regulators through its SH3 domains, including N-WASP (Frischknecht *et al*., 1999; Gruenheid *et al*., 2001). EPEC and vaccinia virus both exploit this ectopic recruitment of Nck to induce aberrant actin polymerization, which in the case of EPEC is required for the formation of cell surface protrusions (pedestals) to which the bacterium adheres. A related strategy is employed by the E6 protein of the high-risk human papilloma virus (HPV) to degrade Dlg and Scribble proteins, both of which possess PDZ domains, are involved in controlling apical-basolateral polarity in epithelial cells, and have been implicated as potential tumor suppressors from experiments in *Drosophila* (Figure 3a) (Bilder, 2004; Macara, 2004). The E6 protein of HPV-16 and HPV-18 has a C-terminal motif (E-T-Q-V/L) that recruits these polarity proteins through PDZ domain-based interactions, and targets them for ubiquitination and degradation by the proteosome (Thomas *et al*., 2005). Loss of Dlg and Scribble would be anticipated to disrupt epithelial polarity and enhance proliferation, and might therefore contribute to HPV-induced malignancy.

Oncogenic re-wiring

Chromosome translocations have been observed in a number of human cancers, and provide a mechanism to generate aberrant, chimeric proteins. In such proteins, the regulatory and effector properties of one polypeptide can potentially be drastically altered by its fusion partner. Chimeric oncoproteins can therefore, in principle, re-wire the signaling networks that control cell proliferation and differentiation, thereby contributing to malignancy. As one example, the Bcr–Abl fusion protein is encoded by the Philadelphia chromosome in chronic myelogenous leukemia (CML), resulting from a reciprocal t(9;22) chromosome translocation that fuses the N-terminal region of the Bcr protein to the C-terminal sequence of the Abl cytoplasmic tyrosine kinase (Figure 4a) (Rowley, 1990). The N-terminal Bcr region alters both the catalytic activity and signaling output of the truncated Abl tyrosine kinase, which comprises an SH3 domain, an SH2 domain, the kinase domain and a non-catalytic tail. Bcr contains a coiled-coil sequence that forms a tetramer, and thereby promotes autophosphorylation and activation of the linked Abl kinase domain (McWhirter *et al*., 1993). In addition, the N-terminal region of Bcr has a tyrosine residue (Y177) located in an optimal-binding motif (YVNV) for the SH2 domain of the Grb2 adaptor. In the context of the Bcr–Abl chimeric protein, Y177 becomes highly phosphorylated, and consequently recruits Grb2, and proteins associated with the Grb2 SH3 domains, such as Sos (a Ras GEF) and Gab2 (a scaffolding protein that is phosphorylated by Bcr–Abl and in turn binds PI 3′-kinase) (Pendergast *et al*., 1993; Puil *et al*., 1994). In a mouse model system, a mutant of human Bcr–Abl lacking this Grb2-binding site is greatly attenuated in its ability to induce a CML-like myeloproliferative disease (Million and Van Etten, 2000), as is a mutant lacking the Bcr coiled-coil region (He *et al*., 2002). Furthermore, Bcr–Abl is unable to transform myeloid progenitors lacking Gab2, indicating that the Bcr–Abl/Grb2/Gab2/PI

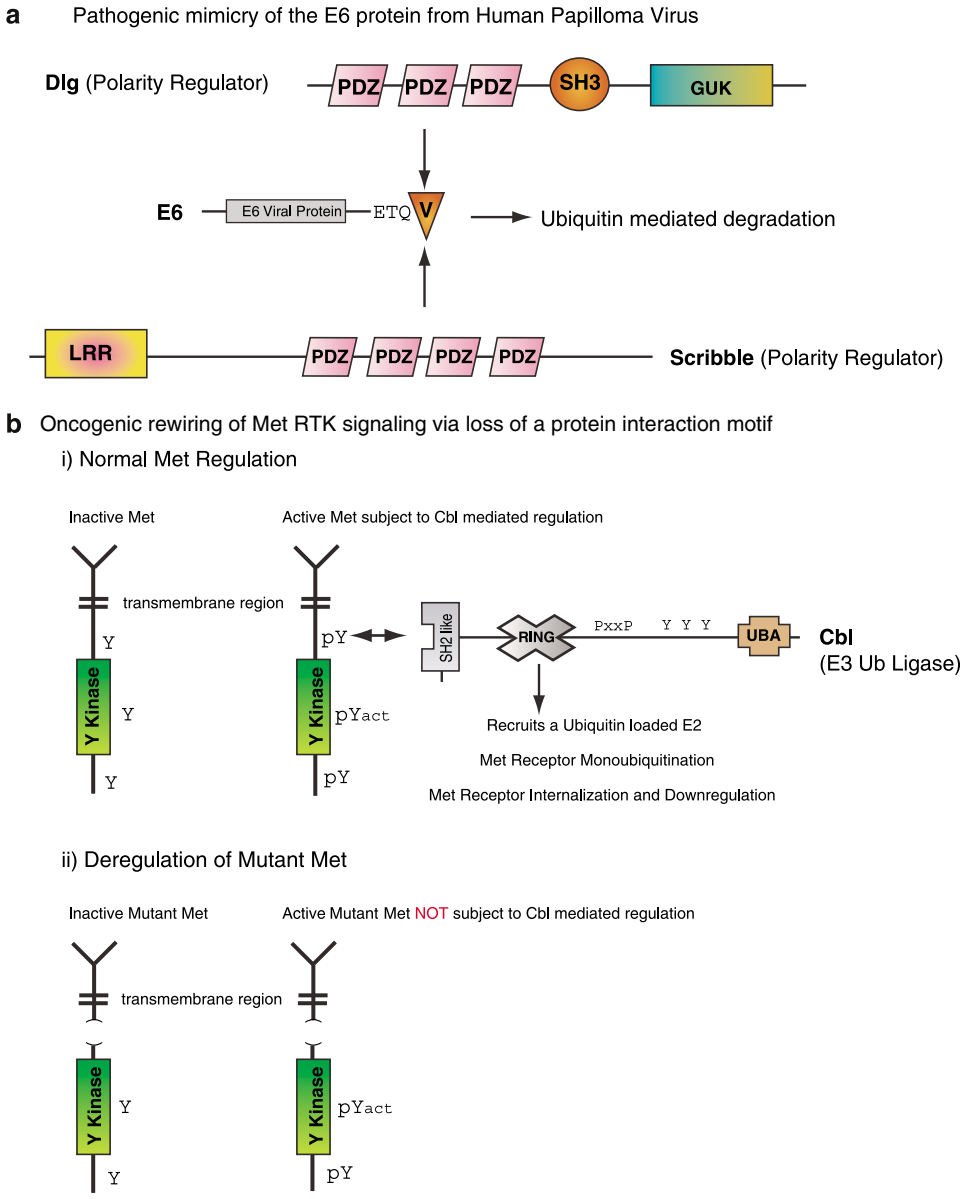

Figure 3 The presence and absence of interaction motifs alter protein regulation. (**a**) The C-terminal PDZ domain binding motif of the E6 protein encoded by the high risk HPVs (HPV-16 and HPV-18) targets the polarity regulators Dlg and Scribble for ubiquitin-mediated degradation. In the case of Dlg, the second PDZ domain recognizes the C-terminal PDZ domain-binding motif of E6. (**b**) Somatic mutations identified from human lung cancer patients in the regulatory juxtamembrane region of the Met RTK disrupt proper regulation of Met signaling by removing an essential protein interaction motif required to bind the E3 Ubiquitin ligase Cbl. The regulation of normal Met (upper panel) is contrasted with mutant Met (lower panel). Abbreviation: LRR, *L*eucine-*R*ich *R*epeat; pYact represents kinase domain activation loop phosphorylation and kinase activity, a V in a triangle represents a PDZ domain-binding motif. Please see the text for more details on the aberrant regulation of these oncogenic proteins.

3′-kinase pathway is important for the induction of myeloid leukemia (Sattler *et al*., 2002). Recent data indicate that Y177-dependent activation of the PI 3′-kinase pathway leads to an increase in glucose metabolism, and a consequent stimulation of the mitochondrial electron transport chain that increases intracellular reactive oxygen species in a fashion that contributes to transformation (Kim *et al*., 2005). Taken together, these results indicate that the pathogenic fusion of Bcr to Abl results in a series of aberrant protein–protein and protein–phospholipid interactions that lead to the transformation of myeloid progenitors. In particular, the ectopic phosphorylation of the Bcr-encoded Y177 site, and its recognition by the Grb2 SH2 domain, likely expands the signaling range of Bcr–Abl in a fashion that contributes strongly to malignancy. In this sense, signaling pathways are re-wired in Bcr–Abl-transformed cells.

In addition to their importance in mediating the malignant effects of Bcr–Abl, interaction domains also

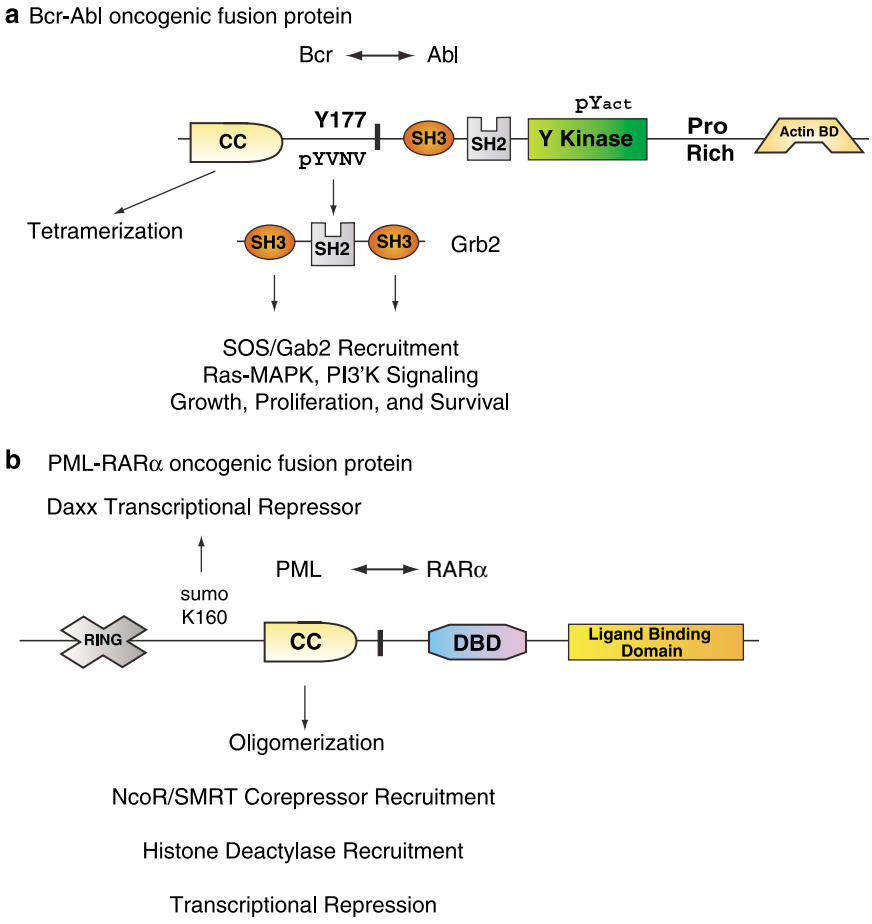

Figure 4 Chromosomal translocations can give rise to oncogenic fusion proteins. The modular domain structure of the Bcr–Abl (**a**) and PML–RARα (**b**) oncogenic fusion proteins are shown. Abbreviations: BD, *B*inding *D*omain; CC, *C*oiled-*C*oiled domain; DBD, *D*NA *B*inding *D*omain; pYact represents kinase domain activation loop phosphorylation and kinase activity. Please see the text for more details regarding the molecular events leading to the oncogenic activation of these fusion proteins.

contribute to the suppression of Bcr–Abl kinase activity imposed by the small molecule inhibitor, imatinib. Oncogenic cytoplasmic tyrosine kinases have been known for some time to have the capacity to toggle between active and inactive conformations (Weinmaster *et al*., 1984). Imatinib binds selectively to the Abl kinase domain in its inactive state, by recognizing an auto-inhibited conformation that is normally shaped by the intramolecular interaction of the catalytic domain with the adjacent SH2 and SH3 domains (Nagar *et al*., 2003). The selectivity with which imatinib inhibits Abl, as opposed to Src, is due to the distinct conformations of the autoinhibited enzymes, which in turn results from differences in their interactions with their linked SH2 and SH3 domains.

The ectopic engagement of signaling pathways by oncoproteins is not necessarily dependent on the formation of chimeric polypeptides. In the case of ErbB2 amplification in human breast cancer, there are typically no sequence alterations in the overexpressed ErbB2 RTK, which becomes activated because of the high density of receptor at the cell surface. However, elevated levels of the receptor may result in the promiscuous recruitment of non-physiological targets. This is suggested by a study in which the binding of phosphopeptides from ErbB/epidermal growth factor (EGF) receptor family members to a majority of human SH2 domains was quantitated, using an array-based format (Jones *et al*., 2006). Of interest, as the affinity threshold for the binding of SH2 domains to ErbB2 was weakened, these interactions became much more diverse, suggesting that amplified ErbB2 might recruit targets in addition to those bound in normal cells, and thereby extend its signaling repertoire. A similar observation was made for the EGF receptor, but not ErbB3, consistent with the frequent overexpression of ErbB2 and the EGF receptor in human cancers.

A somewhat similar effect may be achieved as a result of an RTK losing a c-Cbl recruitment site. Cbl pro teins are E3 protein-ubiquitin ligases with a variant SH2 domain, through which they are recruited to specific RTK autophosphorylation sites to induce receptor ubiquitination, and consequent downregulation (Haglund and Dikic, 2005). In principle, loss of the Cbl-binding site should stabilize the receptor at the cell surface, and thus prolong its signaling at the plasma

membrane. Indeed, mutations detected in the Met RTK in lung cancer can lead to a deletion of the Cbl-binding motif in the juxtamembrane region of the receptor, and thus prolonged residence of the receptor at the plasma membrane and sustained extracellular signal-regulated kinase MAP kinase activation (Figure 3b) (Kong-Beltran *et al*., 2006). In this case, the severing of a regulatory connection likely promotes inappropriate kinetics of Met signaling.

The preceding examples involve fusions, mutations or amplifications involving tyrosine kinases, but rather similar arguments can be made for other classes of oncoproteins, such as nuclear transcription factors, which are commonly expressed in the form of chimeric oncoproteins following reciprocal chromosome translocations in leukemia. For example, in acute promyelocytic leukemia (APL), the gene encoding the retinoic acid receptor α (RARα) is joined to a partner, which in at least 90% of cases is PML, leading to the expression of a PML–RARα chimeric protein (Figure 4b) (Minucci *et al*., 2001). The fusion of PML to RARα silences the ability of RARα to activate target genes involved in myeloid differentiation. This activity of PML appears dependent on its ability to oligomerize, which in turn promotes association of the PML–RARα fusion protein with transcriptional corepressors (NcoR/SMRT) that recruit histone deacetylases to inhibit gene expression through effects on chromatin organization. Furthermore, K160 in the PML moiety of PML–RARα is sumoylated, forming a binding site for the transcriptional repressor Daxx and promoting the APL phenotype (Zhu *et al*., 2005). This potent engagement of transcriptional repressors likely explains why PML–RARα, unlike endogenous RARα, is not able to stimulate transcription in response to physiological levels of retinoic acid (RA). PML therefore converts RARα from an activator of gene expression during hematopoietic differentiation into a transcriptional repressor. However, supra-physiological levels of RA can overcome this effect, and thereby reverse the leukemic phenotype. Recent work also indicates that PML expands the repertoire of DNA sites that can be engaged by the RARα DNA-binding domain, in a fashion that contributes to transforming activity (Zhou *et al*., 2006). PML therefore endows RARα with novel transcriptional and regulatory properties that re-wire gene expression in hematopoietic cells.

Conclusion

The results summarized above lead to the following view of signal transduction in normal and cancer cells. Signaling pathways are usually controlled through a precise network of protein–protein interactions, involving modular interaction domains and their cognate binding motifs. These interactions are frequently regulated by post-translational modifications such as phosphorylation, ubiquitination or sumoylation, among others. Oncogenic mutations, gene fusions and amplifications can disturb the fine balance of signaling networks, resulting in ectopic interactions, which promote transformation. On the other side of the coin, small molecules that can reverse these aberrant states (i.e. converting PML–RARα to an active state with RA, or Bcr–Abl to an inactive conformation with imatinib), provide one approach to targeted cancer therapy.

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