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Account/Revue

Targeting protein–protein interactions, a wide open field for drug design

Inhiber les interactions protéine–protéine, un large champ ouvert pour le développement de nouveaux médicaments

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ABSTRACT

Targeting protein–protein interactions has long been considered as a very difficult if impossible task, but over the past decade, front lines have moved. The number of successful examples is exponentially growing. This review presents a rapid overview of recent advances in this field considering the strengths and weaknesses of the small molecule approaches and alternative strategies such as the selection or design of artificial antibodies, peptides or peptidomimetics.

RÉSUMÉ

Cibler les interactions protéine–protéine a longtemps été considéré comme une tâche très difficile, voire impossible, mais, depuis les dix dernières années, les lignes ont bougé. Le nombre d'exemples de réussites s'accroît exponentiellement. Cette revue présente un rapide panorama des avancées récentes dans ce domaine, considérant les forces et les faiblesses de l'approche « petite molécule » ainsi que des stratégies alternatives comme la sélection ou le design d'anticorps artificiels, de peptides ou de peptidomimétiques.

1. Introduction: targeting protein–protein interactions

Pharmaceutical R&D undergoes a decline of productivity as the number of new drugs approved by the FDA regularly decreases [1, 2]. Besides market forces and difficulties such as demand and competition, pharmaceutical R&D has become increasingly challenging. Advances in the

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understanding of disease mechanisms highlight that complex and multifactorial systems could be dissected in order to identify reliable, safe and effective medicines [3, 4].

The origin of diseases often lies in a complex network of biological interactions that need to be understood not only at a clinical level, but also at phenotypic and molecular levels. In that perspective, a wide range of 'omics' approaches (gene, RNA, protein, metabolism, etc.) have been developed and data are accumulating with the hope that they will become useful for personalized treatments [5]. Among them, proteomic approaches (including yeast two-hybrid, affinity purification coupled to mass spectrometry, and protein complementation assays) led to the establishment of protein–protein interaction (PPI) networks in different model species and several human cell lines. These data are centralized in open-access databases (reviewed in [6]) and are regularly augmented by novel high- and low-throughput experiments [7].

PPI networks are highly interconnected, some proteins behaving as hubs, and involved in a large number of interactions (on average, each protein has 5 partners and hub proteins can associate with more than a hundred partners [8]). A typical example of a hub protein is the human protein p53 shown as a central node in the network in Fig. 1 and which is found mutated in multiple types of cancers. These interaction networks reorganize upon stress and in numerous diseases. Mutations leading to the inhibition of protein functions can also strongly impact PPI networks, but it is still very difficult to predict how far a PPI network can be perturbed by such mutations. Predicting the phenotypical consequences of a mutation in various cell types or tissues also remains out of reach although some studies are progressing toward that goal [9–11]. Interestingly, protein mutants associated with a disease were found to perturb PPI networks in a much larger proportion compared to common variants (whose mutations were not shown to be associated with any disease) [7] suggesting that pathologies could likely be related to the perturbation of PPI networks.

Deciphering the molecular logic associated with PPI networks remains a major challenge for the next decade, not only for fundamental research but also for pharmaceutical R&D. In this line, systematic knock-out or knock-down of genes has been performed at the genome scale in different model organisms of human cell types to analyze functional and genetic interactions between genes [12–15]. However, interpretation is hindered by the difficulty in disentangling the pleiotropic effects of protein depletion. Multiple pathways will likely be affected upon inactivation of a hub protein. In parallel, for decades, pharmaceutical R&D has generated molecules that are able to inhibit the catalytic activity of many protein targets associated with diseases or targeting G-protein coupled receptors (GPCRs) that are the starting point of major and complex cellular pathways. Such molecules can be used as tools to perturb PPI networks and evaluate the associated

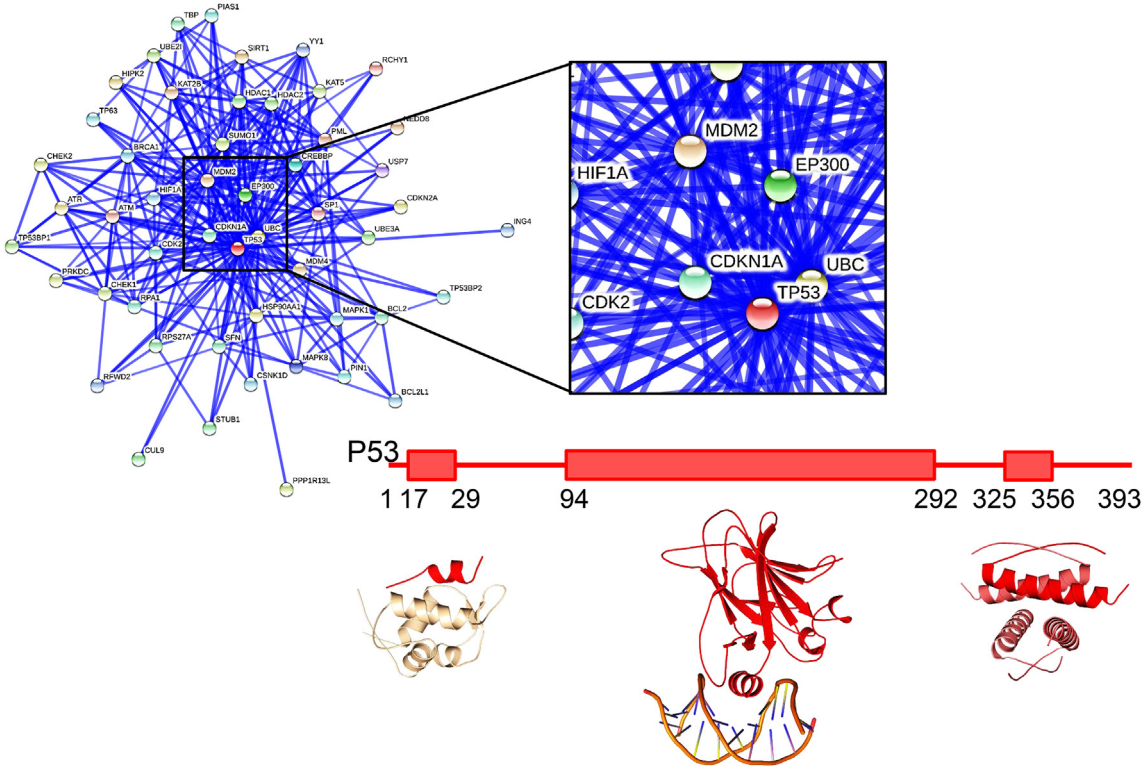

Fig. 1. Interaction network and domain structure of the oncoprotein p53. Interaction network from the STRING database (http://string-db.org) for human p53. The lines indicate interactions between the proteins, with thickness of the lines reflecting confidence in the displayed interaction. The central region around p53 is zoomed in on. The domain structure of p53 and structures of individual domains in interaction with partners are also represented (from left to right: interaction with MDM2, pdb 1ycr [145], DNA, pdb 1tsr 8023157 [146], and self-association, pdb 1c26 [147]).

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