



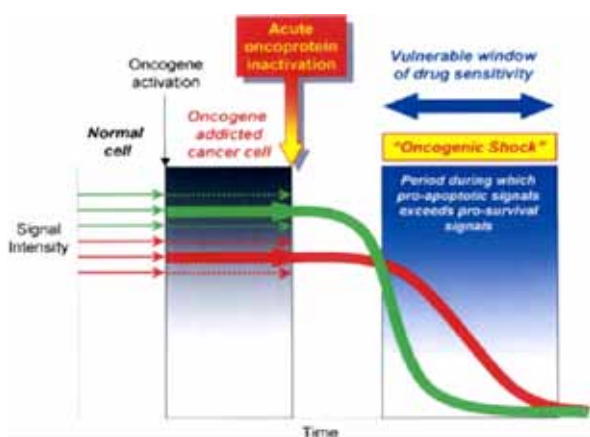
# ONCOGENE ADDICTION MIGHT BE THE ACHILLES HEEL IN CANCER - PART II

## MOLECULAR MECHANISMS OF ONCOGENE ADDICTION

Various hypotheses have been put forward to account for the molecular mechanism of oncogene addiction, with the main ones being synthetic lethality and oncogenic shock. A favoured hypothesis is that of synthetic lethality. Two genes are said to be synthetically lethal if mutation of one of the genes is compatible with cell survival but mutation in both genes results in cell death. It has been suggested that in a cancer cell, the activating oncogene is in a synthetic lethal relationship with a gene that is inactivated in the cancer cell. Accordingly, eliminating the oncogene would lead to cancer cell death<sup>32,33</sup> while sparing normal cells. Using this fact to their advantage, Puyol et al.<sup>34</sup> unveiled a therapeutic strategy for non-small cell lung carcinoma after discovering that a synthetic lethal interaction exists between K-Ras oncogenes and Cdk4.

One other favourite mechanism that has also been put forward to explain oncogene addiction is referred to as 'oncogenic shock'. Here, Sharma et al.<sup>35</sup> proposed that the acute inactivation of the oncogene protein (oncoprotein), results in a 'differential decay rates of various prosurvival and proapoptotic signals' associated with the oncoprotein (figure 1). Indeed, they suggested that the prosurvival signals (green arrows) are transient and dissipate relatively quickly upon oncogene inactivation, whereas the proapoptotic signals (red arrows) linger for a longer period of time thus committing the tumour cell to apoptotic death.

Consistent with this model, Sharma et al.<sup>35</sup> observed that when lung cancer cells are treated with gefitinib, which, like erlotinib, is an epidermal growth factor receptor (EGFR) inhibitor, they are more efficiently killed than when they are treated with the prosurvival receptor ligand, EGF.



**Figure 1.** Relationship between oncogene addiction and oncogenic shock. In an oncogene addicted cancer cell, the prosurvival signals (green arrows) predominate over the proapoptotic signals (red arrows) and result in the survival of the cancer cell. Following acute oncoprotein inactivation, prosurvival signals dissipate rather quickly relative to the proapoptotic signals which are prolonged. Thus the lingering proapoptotic signals cause the cells to irreversibly undergo apoptosis (Source: Sharma and Settleman, 200736).

## INTEGRATING NEW APPROACHES INTO THE CLINICAL SETTING IN ORDER TO CHARACTERISE THE STATE OF ONCOGENE ADDICTION

Identifying the particular state of oncogene addiction in specific types of human cancer can be conducive to treating patients with appropriate molecular agents. Presently, there is no way to fully assess the total signalling pathways, inside and outside normal or cancer cells, that control their proliferation, differentiation and apoptosis. However, advances are being made in profiling patterns of gene expression, genomics, epigenomics, proteomics, network theory, systems biology and computer modelling. These advances will eventually help in identifying the Achilles' heel in specific types (and their subtypes) of human cancer. Integrating all these techniques would then lead to tailor-made optimal therapy by developing agents that target the critical oncogene. Also they would become useful in 'oncogenic escape' states.

Cancers can 'escape' from a particular state of oncogene addiction. This results due to mutations in other genes and pathways, probably because of the genomic instability of cancers. Moreover, many research papers, such as that by Giuriato and Felsher,<sup>37</sup> even suggest that upon sustained oncogene inactivation, some cancers relapse and are thus no longer dependent on the oncogene to which they were previously addicted to. This explains why using single molecular targeted agents may not achieve long-lasting remissions or cures and one needs to opt for combination therapies in such situations. But again combination therapies should be rationally designed using the integrative approaches mentioned above.

Currently, choosing the best molecular targeted agent, alone or in combination, for a specific patient with cancer is largely empirical. But this scenario is rapidly changing, as the oncologist can now choose from a rapidly developing list of diverse molecular targeted agents. This coupled with several research mechanistic studies and techniques to profile the molecular networks in human cancer and their subtypes, should exploit the concept of oncogene addiction and be conducive to more rational, effective and tailor-made therapies for cancer.

## CONCLUSION

Cancer is multifaceted, involving many interactions between different genes, pathways and signalling cascades. This makes the detection of a single marker molecule, and thus the determination of oncogene addiction, rather complex. Besides, it has also been reported by Tonon<sup>38</sup> that genetic abnormalities in cancers tend to gather around specific pathways, giving way to the concept of 'network addiction', rather than oncogene addiction. Therefore, the development of new integrative strategies for defining these oncogene addiction networks together with the use of molecular target agents, might, in the near future, make it possible to achieve more effective, tailor-made therapies for the treatment of human cancer. ❄️