SCIENTIFIC COMMENTARIES

Vascular endothelial growth factor and HDAC 6: a neuroprotective signalling pathway against cancer therapy-induced neuropathy

In the context of treatments for cancer, the use of chemotherapeutic agents focuses on arresting cell division, anti-angiogenesis and targeting mechanisms responsible for metastasis. For that purpose, treatments are designed to manipulate molecules that impair each of these processes by inhibition of signalling pathways and growth factor receptors, as well as changing the dynamics of cytoskeletal proteins involved in cell division and migration. However, chemotherapeutic drugs affect not only tumour cells but also the physiology of other host tissues, including neurons: specifically, anti-cancer drugs exert direct and indirect effects on sensory nerves. Peripheral neuropathies result from dysregulation of mechanisms controlling neuronal physiology and myelination. Toxic neuropathies caused by chemotherapeutic agents are prominent amongst the many genetic and non-genetic causes of neuropathy (von Hehn et al., 2012).

The mechanisms involved in neuropathy associated with the use of paclitaxel include terminal armour degeneration, mitochondrial changes, inflammation, activation of calpain and caspases and changes in the expression and function of calcium, sodium and potassium voltage-gated ionic channels (Jaggi and Singh, 2012). These changes may predispose to profound loss of motor and sensory function with pain. Paclitaxel binds to beta-tubulin and stabilizes its polymerization, disrupting the dynamics of microtubules, arresting cell division and activating apoptotic pathways. Paclitaxel also increases tubulin acetylation, which has several consequences on physiological and pathological processes (Polomano et al., 2001). Tubulin acetylation impacts on subcellular organelles, and vesicular traffic and signalling that control the localization and movement of plasma membrane proteins (Janke and Bulinski, 2012). Tubulin acetylation also affects the affinity of motor proteins and, in this sense, is critical for neuronal development and function. While the mechanisms governing tubulin acetylation are not completely known, tubulin deacetylation is carried out by histone deacetylase 6 (HDAC6). This deacetylase is involved in both neuronal developmental processes (Tapia et al., 2010) and neurodegenerative disorders (such as Huntington’s or Parkinson’s diseases; Li et al., 2011). Its loss of function affects emotional behaviour in mice, especially increasing hyperactivity (Fukada et al., 2012). Among the several substrates that HDAC6 can deacetylate, heat shock protein 90 (Hsp90) is an essential chaperone involved in cell migration and survival. Molecules that target HDAC6 (tubacin) and Hsp90 (17-AAG) have also been studied as potential chemotherapeutic drugs (Rao et al., 2008).

Other therapeutic approaches against tumours use monoclonal antibodies directed against the vascular endothelial growth factor (VEGF) receptor to impair angiogenesis. VEGF is one of the most studied growth factors related to angiogenesis and metastasis, and chemotherapeutic strategies have been developed based on VEGF receptor-neutralizing monoclonal antibodies, such as bevacizumab. In fact, VEGF and its receptors have multiple functions in cell physiology, controlling migration and angiogenesis. While useful for certain types of tumours, anti-VEGF/VEGF receptor therapies may lead to a variety of adverse effects, including peripheral neuropathies and cerebral disorders. For example, a small proportion of patients treated with VEGF/VEFG receptor inhibitors develop posterior reversible encephalopathy syndrome associated with brain oedema. The presentation of this syndrome ranges from headache to changes in mental status, seizures and blindness (Chen and Cleck, 2009).

VEGF binds to the tyrosine kinase receptors VEGFR-1 (Flt-1) and VEGFR-2 (Flk1). VEGF has several functions in neural cells independent from its role in vessels. It is mitogenic for astroglia and Schwann cells, promotes neurogenesis, neuronal migration, neuronal survival, axon guidance and synaptic plasticity (Mackenzie and Ruhrberg, 2012). In cultured neural cells, VEGF stimulates axonal growth and increases survival of neuronal and satellite cells. Inhibition of VEGF-2 (Flk1) in dorsal root ganglia blocks axonal growth. These neurotrophic effects are also observed in the CNS, increasing the survival, growth and density of astrocytes and neurons. Moreover, VEGF is neuroprotective against glutamate-induced toxicity, activating the PI3-kinase/Akt and MAP kinase pathways. Knock-in mice that lack a functional VEGF promoter in neuronal tissue suffer severe adult-onset muscle weakness due to degeneration of lower motor neurons, symptoms that are reminiscent of those observed in amyotrophic lateral sclerosis. VEGF has also been implicated in diabetic neuropathy, ischaemia and nerve regeneration (Carmeliet and Storkebaum, 2002). While the role of VEGF in angiogenesis in
the nervous system is clearly demonstrated, increasing evidence also supports its role in several neurological processes and disorders. Understanding the role of VEGF and its signalling pathway will allow us to evaluate how the modulation of its signalling pathway can be used therapeutically.

Against this background, in the present issue, Verheyen et al. (2012) report that systemic anti-VEGF therapies induce a painful sensory neuropathy (see page 2629). They show that mice treated intraperitoneally with an antibody directed against the VEGFR-2 (Flk1), DC101, develop tactile allodynia and thermal hyperalgesia. Similar results are obtained in mice treated with a VEGFR tyrosine kinase inhibitor (SU5416). In both cases, symptoms gradually disappear after discontinuing the injections. Anti-VEGFR is used clinically in combination with paclitaxel, and the authors show that anti-VEGFR treatment is additive to the effect of paclitaxel in increasing tactile allodynia and tubulin acetylation. Using transgenic mice that overexpress Flk1 or a dominant negative form of Flk1 in neurons, they report that Flk1WT mice show no increase in tubulin acetylation after paclitaxel treatment and gradually recover after DC101 or paclitaxel is withdrawn, whereas Flk1DN mice show a further increase in acetylation and fail to recover after combined treatments. To understand this additive effect and the signalling pathways affected by anti-VEGFR treatments, they use a model of cultured peripheral neurons (dorsal root ganglia). In this situation, VEGF treatment restores neuronal survival and acetylation levels in neurons treated with paclitaxel, as happens in neurons from Flk1WT mice. The authors propose that this beneficial effect depends on HDAC6 (histone deacetylase 6 or tubulin deacetylase 6) activity, since inhibition of HDAC6 with tubacin impairs the partial recovery mediated by VEGF treatment. They conclude that HDAC6 activity is necessary to increase the anti-apoptotic protein Bcl2, probably by means of Hsp90 deacetylation, as Hsp90 inhibition impairs the neuroprotective effects of VEGF in the presence of paclitaxel. This signalling pathway is supported by their results indicating that HDAC6 overexpression inhibits the increase in tubulin acetylation induced by anti-VEGFR antibody, as well as the reduction in Bcl2 expression.

It is clear from these data that one mechanism whereby some cancer-chemotherapeutic drugs induce painful neuropathy, which often limits therapy, is the modification of acetylation. The data presented by Verheyen et al. suggest a role of HDAC6 in the neuroprotection induced by VEGF to reverse adverse effects generated by paclitaxel or anti-VEGFR therapies. In this sense, it has been postulated that HDAC6 can be regulated by glycogen synthase kinase 3 (GSK-3; Chen et al., 2010). Moreover, HDAC6 is necessary to regulate sodium channel concentration at the axon initial segment, and to maintain the differential characteristics of microtubules in axonal domains (Tapia et al., 2010). In fact, some data indicate that anti-cancer drugs trigger changes in sodium channel expression/function that alter the function of calcium channels, increasing neuronal excitability and responsiveness of nociceptors in dorsal root ganglia neurons, thus contributing to the pathogenesis of neuropathic pain (Jaggi and Singh, 2012). Therefore, understanding how HDAC6 is regulated in neuronal cells is essential in order to find a combined therapeutic approach that compensates for secondary effects damaging sensory nerves in the context of chemotherapy for cancer.

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