Commentary

Is IL-6 Both a Cytokine and a Neurotrophic Factor?

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The article by Hirota et al. (pp. 2627–2634) provides interesting evidence for the action of Interleukin-6 (IL-6) in the nervous system, but is it appropriate to consider IL-6 a neurotrophic factor; and, if so, what does this mean? The last decade has seen the discovery of a large number of neurotrophic and neural differentiation factors in both the peripheral and central nervous system. Examples of peptides with interesting activities in the nervous system include BDNF, NT-3, CNTF, GDNF, bFGF, aFGF, IL-3, IL-2, LIF, and others. The molecular characterization of growth factors has led to the realization that these peptides can play different roles in the nervous system and that they can also play important roles in many other tissues.

Over the last 40 years, studies of Nerve Growth Factor (NGF), which is the prototypic growth factor, have demonstrated that NGF plays a central role in the development and survival of neurons from both the peripheral and central nervous system. NGF functions as a target derived trophic factor, i.e., a factor that is derived from an innervated tissue that is essential for the survival of the innervating neuron. Competition for trophic factors, which are thought to be in limiting supply, is believed to be a major cause of apoptotic cell death, a feature of almost every developing neuronal population. Over the past few years, studies using gene disruption approaches (1) have confirmed and extended the classic immunosympathectomy experiments (2) that used antibodies directed against NGF to show its importance in the development of the peripheral nervous system.

More recently, functional NGF receptors have been documented in T cells, B cells and mast cells (e.g., see references 3, 4, 5, and references therein). Both NGF and IL-6 affect stromal cells in the thymus and may participate in a neuromodulatory loop (6). These experiments support the possibility that peptide growth factors could mediate interactions both within and, possibly, between the nervous system and the immune system.

Another class of peptides important in the development of the nervous system were originally studied because they served an instructional rather than a survival role. For example, the developing sympathetic nerve expresses both cholinergic and adrenergic characteristics, but during the process of innervation, the choice of neurotransmitter is fixed in a process that depends on the target of innervation (for reviews see references 7, 8). A similar change has been shown to occur in cultured sympathetic neurons. This allowed investigators to purify the environmental factors that could participate in this switching event. These studies led to the purification of the first cholinergic differentiation factor (CDF), which, surprisingly, was identical to the previously described Leukemia Inhibitory Factor (LIF) (9). While there is no doubt that CDF/LIF can influence the expression of classic neurotransmitters and neuropeptides, studies with mice deficient in the expression of this peptide demonstrate that it is not essential for determining neuronal phenotype in all cases. Interestingly, CDF/LIF is induced during neural injury and can rescue motor neurons from axotomy induced cell death, blurring the distinction between trophic (i.e., survival) and instructive factors (10, 11).

CDF/LIF is homologous to ciliary neuronotrophic factor (CNTF), which was purified as a survival factor for cholinergic neurons in the peripheral nervous system, but it may also play a role in the central nervous system (12, 13). The timing of the expression of this protein, however, makes it obvious that it could not function as an essential target derived trophic factor (14). Both CNTF and LIF are homologous to IL-6, a peptide that was isolated as a factor that stimulates B cell differentiation into immunoglobulin secreting cells. There is, however, emerging evidence that IL-6 has roles both in the immune function and the nervous system. All three factors use gp130 as part of their cell surface receptor.

The discovery that IL-6 was expressed in astrocytes led to speculation that it might play a role in the nervous system (15). Initial studies demonstrated that IL-6 could stimulate the differentiation of PC12 cells as demonstrated by the elaboration of neurites (i.e., long nerve-like processes), the development of action potentials, and the expression of a number of neuronal markers. All of these are responses that are also controlled by classic neurotrophic factors like NGF. Furthermore, IL-6 activates many of the same intracellular signaling events that are activated by NGF (16, 17). These initial observations inspired the search for other roles for this growth factor in the nervous system.

Since one of the hallmarks of trophic factors is their ability to promote neuron survival, a number of studies of the protective effects of IL6 have been done. IL-6 protects dopaminergic neurons against MPP+ (1-methyl-4-phenylpyridinium) toxicity (18) and the development of a Parkinson-like syndrome, and it protects striatal neurons against NMDA (*N*-Methyl-D-Aspartate), a neurotoxic glutamate an-

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alog that acts at the NMDA receptor (19). IL-6 can enhance the survival of several classes of neurons in culture (20, 21).

IL-6 alone is not capable of stimulating neurite outgrowth from cells in the peripheral nervous system, which is surprising since the PC12 line mostly resembles an uncommitted sympathetic nerve. However, IL-6 can influence the expression of neurotransmitter enzymes, which is consistent with its structural and functional homology to LIF/CDF (22). IL-6 and its receptor have been shown to be induced in response to neural injury, again suggesting that IL-6 is part of a coordinated response to injury in the adult (23, 24).

The paper by Hirota and colleagues in this issue (pp. 2627–2634) makes several important contributions to this emerging story. First, it demonstrates that the failure of at least some sensory nerves to respond to IL-6 is the lack of the IL-6 receptor. Presumably, IL-6 and the soluble form of the IL-6 receptor interact and activate the gp130 receptor as a complex. Thus, the addition of the soluble IL-6 receptor allows these cells to respond to IL-6. This observation parallels the effectiveness of the combination of IL-6 and its receptor in several other systems (25). This somewhat unusual situation has been described mechanistically as a two chain receptor model (26); but it also has interesting biological implications which merit future consideration. The failure of a neuron to express the IL-6 receptor under normal circumstances would allow them to express gp130, which also serves as a receptor for CNTF and LIF, allowing them to retain responsiveness to these growth factors. It provides an insight into the striking similarity of the effects of CNTF, LIF/CDF and IL-6 as well as an interesting explanation of the differences among these peptides. The involvement of a second receptor subunit in defining receptor specificity is reminiscent of the role of p75 in modulating the specificity of the NGF receptor (27).

Several peptide growth factors, including NGF and FGF have been shown to enhance peripheral nerve regeneration, and since IL-6 acts by a different receptor class there is an exciting possibility for synergistic stimulation of regeneration and regain of physiological function. Likewise, IL-6/IL-6R or related growth factors might provide trophic support for neurons in a variety of neurodegenerative diseases (28).

As in the case of the LIF and CNTF, the capability of a peptide to regulate a particular biological response does not necessarily mean that it does so in vivo. In this paper, the biological relevance of IL-6's in vitro activity was strengthened by the demonstration that antibody to IL-6R inhibited regeneration. This suggests that endogenous activity of this pathway promotes regeneration. Furthermore, nerve injury also increased the expression of IL-6R in the damaged nerve making it more likely to be responsive to IL-6. Likewise, there is an increase in the expression of IL6 in the supporting Schwann cells. Nerve injury also enhances production of NGF in Schwann cells, indicating that they are capable of providing several classes of trophic support. In the context of studies with the clonal lines cited above, there is a strong case for the direct action of IL-6 on regenerating neurons, although the possibility that there is an intermediate cell still exists.

Does IL-6 also play a role in normal development? Does it function as a target derived neurotrophic factor? Current studies make this a pressing question. Studies of its spatial and temporal expression during development should provide circumstantial evidence of whether it might participate in the regulation of apoptotic death during development, or is more likely to be involved in an injury response. More definitive studies will require the use of animals with disrupted genes to determine if aberrant expression of IL-6 and/or its receptor effects neural development. A persuasive case can be made that it might be quite productive to determine the trophic effects of related cytokines including Oncostatin M, which has not yet been studied. Alterations that might be expected could be confined to details of neural phenotype, but may extend to neuronal survival.

Perhaps one of the most intriguing questions raised by these discoveries is whether the presence of common components of cell–cell signaling pathways in the nervous system and the immune system points to a mutual interdependence of these systems during neural regeneration. Nerve regeneration is a complex process that involves the participation of cells from the immune system. In the peripheral nervous system, macrophages play an important role in the regenerative process. Does the expression of IL-6 play a role in modulating the participation of the immune response in regeneration or is it more appropriately viewed as an example of the use of the same signaling components in two systems? There is no doubt that the study of the involvement of cytokines in neural development will continue to be fruitful avenue of exploration.

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