Abeta-mediated crosslinking may regulate TrkA-p75 association and cooperations of p75 with APP, prion and synuclein

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The Abeta-crosslinker-hypothesis (full original text, pdf 1.4 MB) presents evidence for a previously unknown binding site for Abeta on the juxtamembrane stalk region of p75. It proposes that Abeta can crosslink p75 with proteins such as APP, prion and alpha-synuclein and thereby mediate direct trophic and protective cooperations of p75 with these proteins; the known cooperations with the Nogo receptor and Sortilin have restrictive or apoptotic effects and may use Abeta as crosslinker, too. Abeta-mediated crosslinking can be regarded as a means of receptor networking (like certain scaffold proteins) which permits interconnection of signaling processes and by modulation of neurotrophin receptor signaling influences many aspects of cell life. The assumed crosslinking mechanism, however, also allows the binding of pathological Abeta aggregates to the stalk of p75, which can prevent trophic and protective cooperations of p75 and activate detrimental p75 signaling; moreover, pathological aggregates of other amyloidogenic proteins that interact with Abeta (e.g. aggregates of prion, synuclein, SOD1 and amylin) could also bind and activate p75 in this way, with the consequence that a shared mechanism of p75 activation may play a harmful role in different degenerative diseases. The detrimental activation of p75 might be decreased or prevented by suitable fragments or derivatives of the "stalk binding site" of p75 for Abeta. Such Abeta-neutralizing derivatives might be used for the treatment of several degenerative diseases and could have a natural functional equivalent in the p75 segment between the alpha and gamma cleavage sites of the receptor which is released by proteolysis of activated p75. The hypothesis is fully consistent with the scientific literature and largely distilled from it.

Since publication of the hypothesis in autumn 2008 new data have been reported that affect this hypothesis and that have been interpreted in an updated overview of the hypothesis. Two of these reports (Bulbarelli et al., 2009, and Matrone et al., 2009) give rise to an extension of the hypothesis in the sense that Abeta may also crosslink p75 and TrkA receptors and thereby modulate neurotrophin receptor signaling.

Bulbarelli et al. show that administration of (proapoptotic) Abeta25-35 or oligomeric Abeta1-42 to primary cultures of hippocampal neurons produces a temporary and marked elevation of NGF release, TrkA protein, NGF RNA and TrkA RNA, and of TrkA, Akt and GSK3beta phosphorylation; the observed TrkA activation is largely NGF-induced and partly independent of NGF. The investigation raised the question whether NGF and TrkA upregulation might be a defence mechanism against increased Abeta or part of a proapoptotic response to Abeta. Matrone et al. found in NGF-dependent cultures of hippocampal neurons that NGF withdrawal causes an increase in Abeta that leads to proapoptotic signaling of TrkA. Their results also indicate a direct interaction of TrkA, p75 and Abeta and a role of multiprotein TrkA-p75 complexes in this apoptosis. According to their interpretation, NGF withdrawal causes an imbalance of beta and gamma secretase activities that induces apoptosis by increased levels of Abeta and of p75 fragments and by Abeta- and p75-mediated TrkA signaling. The model presented here suggests that crosslinking of TrkA and p75 by increased Abeta, transactivation of TrkA by an associated p75 signaling complex and suppression of prosurvival TrkA signaling by p75-induced ceramide accumulation may underlie the observed proapoptotic TrkA activity.

The following considerations refer to results by Matrone et al. if not indicated otherwise. The striking increase in Abeta upon NGF withdrawal could in part be due to a ceasing of the inhibitory influence of NGF-stimulated TrkA on beta cleavage of APP, and a ceramide-dependent stimulating effect of

(Abeta-)activated p75 on this cleavage (cf. Costantini et al., 2005, and Puglielli et al., 2003); since NGF administration elevates TrkA expression (Kojima et al., 1995) and consequently inhibition of beta cleavage by TrkA, Abeta production might react to NGF withdrawal with a rebound effect. The findings that the increased association of TrkA with p75FL (full-length p75) and p75CTF (the C-terminal fragment that is generated by alpha cleavage of p75) depends on Abeta, and that p75 coprecipitates with TrkA and p75CTF with Abeta, hint that endogenous Abeta could induce such complex formation by direct intervention. Zampieri and Chao (2006) supposed that the association of p75 with TrkA might be mediated by sequences in the stalk domain of p75 and that these sequences "might also play a pivotal role in controlling the association of p75 with its co-receptor partners", while Jung et al. (2003) reported that TrkA-p75 association requires the transmembrane domain of p75; TrkB-p75 association, on the other hand, might be independent of the transmembrane domains of TrkB and p75 (Bibel et al., 1999). As mentioned above, evidence presented by the Abeta-crosslinker-hypothesis shows that Abeta has - in addition to the known binding site in the neurotrophin-binding region of p75 - a second binding site on p75 in the juxtamembrane stalk region which probably extends into the transmembrane domain and overlaps the section between the alpha and gamma cleavage sites. This stalk binding site for Abeta might reconcile the results by Jung et al. (2003) with those by Zampieri and Chao (2006): if it mediates p75 cooperation with e.g. TrkA then its intersections with the stalk or the transmembrane domain may also do so although less efficiently. Taken together, the given arguments point to a crosslinking of TrkA and p75 by Abeta (non-beta-sheet oligomers), which obviously should depend on the level of Abeta; increased Abeta oligomers might saturate p75 receptors at this binding site and thus facilitate complex formation. However, crosslinking by Abeta need not be the only way of TrkA-p75 association since a ternary complex consisting of TrkA, Kidins220/ARMS and p75 has been described (Chang et al., 2004). If crosslinking of TrkA and p75 really occurs then it apparently does not inhibit cleavage of (activated) p75CTF by gamma secretase as data by Matrone et al. on p75ICD (the intracellular domain of p75) and presenilin 1 prove. In contrast, the binding of unsuitable aggregate species of Abeta to the stalk binding site of p75, resulting from administration or extended overproduction of Abeta, could impair the interaction between p75 and gamma secretase and cause accumulation of p75CTF upon p75 activation and alpha cleavage of p75 (cf. Sotthibundhu et al., 2008). A binding site for Abeta on TrkA implies the possibility that binding of unsuitable Abeta aggregates might hamper TrkA activation by NGF and lead to reduced TrkA expression (cf. Costantini et al., 2005).

Matrone et al. report an almost total interruption of Akt phosphorylation upon NGF withdrawal, which indicates that the survival-promoting TrkA and p75 pathways, in particular the PI3K/Akt pathway, are inhibited. Part of this apparent inhibition might be due to coupling of Akt to increased TrkA multiprotein complexes and gradual dephosphorylation; in addition, high TrkA together with rising Abeta might favor TrkA-p75 association at the expense of (hypothetical) other cooperations of p75 and thus further weaken neuroprotective signaling of p75. However, since the PI3K/Akt pathway is inhibited by elevated cytosolic ceramide (cf. e.g. Arboleda et al., 2009), and since the cell death observed by Matrone et al. depends on Abeta and p75 and both Abeta- and p75-induced apoptosis requires the activation of a sphingomyelinase-ceramide pathway (Malaplate-Armand et al., 2006, and Brann et al., 2002), Abeta should inhibit Akt phosphorylation mainly through activation of p75 and ensuing ceramide production. p75 is also responsible for TrkA phosphorylation after NGF withdrawal as partial silencing of p75 RNA largely reduces cell death and TrkA phosphorylation. CDK5 and Src kinases participate in this phosphorylation, and the same Src kinases that according to Egert et al. (2007) mediate p75 phosphorylation by Abeta aggregates or by NGF might also phosphorylate p75-associated TrkA. CDK5 activation by Abeta, which contributes to Abeta-induced pathology, can be prevented by synthetic non-peptide ligands of p75 (Yang et al., 2008) and might therefore be connected with Abeta-induced p75 signaling. By facilitating p75-induced TrkA phosphorylation, TrkA-p75CTF and TrkA-p75FL complexes should be crucial to the reported proapoptotic activity of TrkA. Under the conditions of elevated ceramide and inhibited PI3K/Akt pathway, activated p75-associated TrkA could support and amplify proapoptotic p75 signaling, presumably through the Ras/Rac/JNK pathway (cf. Egert et al., 2007, and Harrington et al., 2002). As partial silencing of TrkA RNA largely diminishes cell death, the NGF-induced rise in TrkA receptors prior to NGF withdrawal is critical for the observed apoptosis. This suggests that higher TrkA expression may lead to cell degeneration or cell death even at otherwise non-apoptotic Abeta concentrations when Abeta-activated TrkA-p75 complexes tip the balance in favor of apoptosis. In living tissue, NGF and TrkA expression might be upregulated in response to rising, non-lethal Abeta concentrations (cf.

Bulbarelli et al.) and counteract Abeta (and perhaps cause neuronal hypertrophy as reported by Iacono et al. (2008)), but when Abeta further increases it might crosslink a growing proportion of TrkA receptors with p75 and successfully compete with NGF for activation of TrkA-p75 complexes. In this case, it would be interesting to know if significant Abeta-induced TrkA transactivation can downregulate TrkA.

At physiological Abeta levels and generally as long as the p75-induced ceramide signal does not suppress the PI3K/Akt pathway, which is also induced by p75 (Roux et al., 2001), Abeta stimulation of p75 and TrkA-p75 complexes should have neurotrophic and neuroprotective consequences similar to NGF stimulation (cf. Susen and Blöchl, 2005). For the overall effect of Abeta or NGF stimulation, the (possibly predominant) contributions of other cooperations of p75 and of non-associated p75 and TrkA - which depend on the ratio TrkA:p75 - have to be taken into account, too. NGF-mediated activation of TrkA and TrkA-p75 complexes can suppress ceramide production by NGF-stimulated or transactivated p75 through a TrkA-induced PI3K/PKC-dependent mechanism (Plo et al., 2004) if TrkA and TrkA-p75 complexes prevail over independent p75. Then NGF-induced signaling of TrkA-associated p75 should support and amplify the neurotrophic and neuroprotective TrkA signaling (cf. Epa et al., 2004) since ceramide is critical for p75-induced apoptosis (Brann et al., 2002).

Speculative considerations and a few clues suggest, that the p75-binding site of a crosslinking Abeta oligomer might essentially be attributable to an N-terminal section of the Abeta sequence, and the TrkA-binding site mainly to part of the C-terminal rest; the hypothetical binding site of TrkA for Abeta might be found within the transmembrane domain of TrkA and its immediate vicinity. Such binding sites might explain NGF-independent TrkA activation upon Abeta administration in the experiments by Bulbarelli et al.: short stacks of beta-sheet Abeta25-35 or Abeta1-42, presenting symmetric binding sites at their ends, might homodimerize TrkA while non-beta-sheet Abeta1-42 oligomers might cause TrkA-p75 association and activation as described above. Bulbarelli et al. discussed membrane effects of Abeta as a possible cause of NGF-independent TrkA activation.

The presented arguments suggest that Abeta can crosslink TrkA receptors with p75, that p75 stimulation by Abeta induces activation of p75-associated TrkA, and that suppression of the survival-promoting PI3K/Akt pathway by p75-induced ceramide accumulation causes p75-associated TrkA to support and amplify proapoptotic signaling of p75. Complexes of TrkA and p75 receptors can serve both trophic and neuroprotective ends or negative growth control and apoptosis, depending on mutual adjustment of receptor conformation and signaling, on the balance or imbalance of the PI3K/Akt and ceramide pathways, and on the stimulation parameters. By altering, integrating and synergizing signaling properties of TrkA and p75, these complexes can optimize and amplify certain signal transductions and in many cases tip the scales in favor of trophic or negative processes. If Abeta regulates their formation and also crosslinks p75 receptors with other cooperation partners then it could substantially modulate neurotrophin receptor signaling and affect many cellular processes; such crosslinking, however, would also sensitize the neurotrophin receptor system to excess Abeta, as the report by Matrone et al. demonstrates.

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