Neuropeptide Y and Peptide YY

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A description of immunomodulatory properties of neuropeptides NPY and PYY on macrophages in the context of cancer.

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1. Origin and Function

Both NPY and PYY belong to a family of neuropeptides bearing a close resemblance to each other, consisting of 36-amino acids with a unique hairpin turn called the PP-fold [1]. NPY is highly abundant and is found in all levels of the gut-brain axis as well as being highly expressed in the central nervous system where it is widely known for its activity as a regulator of food intake and energy balance [2]. PYY is almost exclusively associated with the digestive system and is predominantly expressed in L cells in the ileal and colonic mucosa and released into the bloodstream post-prandially in proportion to calorie intake [2][3][4][5]. NPY and PYY peptides can also be truncated, yielding the fragments NPY(3-36) and PYY(3-36) [6]. In humans, NPY and PYY's functions are mediated by diverse G-protein coupled Y receptor subtypes, of which seven have been noted, but only four are widely functional (Y1, Y2, Y3 and Y4). NPY(1-36) and PYY(1-36) are thought to bind to all the receptors with an equal affinity, whilst NPY(3-36) and PYY(3-36) exhibit the highest affinity for Y2 [7][8][9].

2. NPY and PYY and Cancer Association

Investigation of PYY and NPY, have collectively revealed that they are implicated in a variety of inflammatory disorders, such as autoimmune diseases, asthma, atherosclerosis, and cancer [10][11][12]. Y receptors have recently attracted attention due to their overexpression in various human cancers, including breast carcinomas and neuroblastomas, creating interest in their use as a possible target for cancer imaging and therapy [13]. The Y receptors mediate tumour development through their direct effect on cancer and endothelial cells promoting tumour cell proliferation, survival, and migration, as well as angiogenesis) [14].

3. NPY and PYY Modulate Macrophage Inflammatory Responses

In macrophages, neuropeptides have been found to exert varying effects depending on the age of the subject. In one of the first studies examining their role in macrophage function, both NPY and PYY were found to increase adhesion, chemotaxis, and phagocytosis in murine peritoneal macrophages, as well as increasing the production of superoxide anions in young adult mice [15]. The authors noted that this effect was produced through the stimulation of PKC due to a significant increase in its activation following NPY and PYY treatment. However, in more aged mice, this effect was potentiated, with chemotaxis and phagocytosis being decreased. These changes have been hypothesised to be dependent on the activity of dipeptidyl peptidase 4, an enzyme that terminates the activity of neuropeptides on the Y1 receptor subtype and whose activity is seen to change with age [16]. This age-dependent impact in modulating the immune response was also found to be true concerning PYY and NPY acting via Y1 receptors to potentiate nitric oxide production in rat peritoneal macrophages, with production being suppressed in older rat cells [17]. Y receptors are known to be widely expressed in immune cells, particularly Y1, which has been found in almost every type of immune cell [18].

The expression of Y receptors is also significantly upregulated after antigen or inflammatory stimulation [19][20][21]. Studies have also demonstrated the ability of neuropeptides to modulate macrophage cytokine secretion. However, contradictory results have been found. Y1 ablation in macrophages has been seen to lead to an increased pro-inflammatory phenotype displaying increased inflammatory response and exacerbated secretion of MCP-1 and TNFα, and a similar response was seen in macrophages isolated from double NPY and PYY knockout mice, suggesting an anti-inflammatory role [22]. Additionally, NPY was shown to decrease the production of TNFα and IL-1β following LPS treatment [23][24] and increase that of TGFβ1 in RAW264.7 cells [25]. In contrast, other studies have reported NPY to increase the production of pro-

inflammatory mediators, with NPY being found to significantly increase the expression of TNFα, C-reactive protein, MCP-1 and reactive oxygen species in RAW264.7 macrophages mediated by the Y1 receptor [26]. NPY has also been shown to stimulate IL-1β secretion in aged animal macrophages [27]. Furthermore, in whole blood cells from healthy subjects, NPY upregulated IL-6, IL-1β and TNFα production [28]. Some suggestions for the observed duality have been differences in species, cell type and cell environment. Additionally, the activation of different Y receptor types is seen to mediate different effects, and there is evidence that along with Y1, Y4 and 5 may also play a role in cytokine modulation [22]. A relatively recent study by Cheng et al. found sympathetic stimulation of prostate cancer cells in vitro led to the release of NPY, which in turn was seen to promote myeloid cell trafficking and increased IL6 synthesis in TAMs, promoting tumorigenesis [29]. However, the connections between neuropeptides, immune regulation and cancerous disease have not yet been fully explored, and indeed it may be found that neuropeptides have divergent effects on immune cells in cancer development as observed in their general effects on macrophage function.

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