CMBN seminar: PML and autophagy in development and disease

Tuesday October 4, 10^{15}-11^{45}, Auditorium A3.3067, Rikshospitalet

10.15-10.45:
Paolo Salomoni (UCL Cancer Institute): The role of the promyelocytic leukaemia protein in neural stem cell regulation and brain tumourigenesis

10.45-11.15:
Ai Yamamoto (Columbia University): Selective macroautophagy in the adult and developing brain: A focus on Alfy

11.15-11.45:
Geir Bjørkøy (University College of Sør-Trøndelag): The Autophagic Response as a Putative Determinant for Disease Preventive or Therapeutic Effects of n-3 Polyunsaturated Fatty Acids

ABSTRACTS

Selective macroautophagy in the adult and developing brain: A focus on Alfy

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Alfy/WDFY3 is a large, WD40 and FYVE domain containing protein that has previously been implicating in the selective macroautophagic degradation of expanded polyglutamine and alpha-synuclein containing aggregates using cell-based systems. We had found that while depletion of Alfy impeded the elimination of aggregates, over-expression of Alfy enhanced their elimination. In order to determine whether Alfy plays a similar role in vivo, we have created mice that possess differing genetic modifications in the Alfy locus. Using these mice, we have set out to fulfill two sets of goals: The first set of goals is to determine whether modulating Alfy levels modify progression in a mouse model of Huntington's disease, a devastating neurological disorder caused by an inheritable polyglutamine expansion mutation in the N-terminus of the protein huntingtin. Since the function of Alfy has not been previously characterized in vivo, our second set of goals is to determine the function of Alfy using both deletion and over-expression based approaches. Early studies have revealed that Alfy plays a critical role in axon pathfinding in the developing central nervous system. In light of these findings we hypothesize that Alfy is most highly expressed in brain because it plays an important role in maintaining proper neuronal architecture by eliminating large, ubiquitinated protein complexes, and not only misfolded or aggregated proteins.

The role of the promyelocytic leukaemia protein in neural stem cell regulation and brain tumourigenesis

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The control of proliferation and cell fate decisions in adult neural stem/progenitor cells (NPCs) is critical for adult neurogenesis in the central nervous system (CNS). Recent studies have demonstrated that adult NPCs can serve as the cell of origin for the most aggressive paediatric and adult brain neoplasm, glioblastoma multiforme (GBM). Within established GBM, a subpopulation of stem-like tumour-initiating cells is believed to underlie disease progression. Revealing the mechanisms underlying cell fate control within normal and neoplastic neural stem cells is therefore key to understanding tumour initiation and progression in the CNS. The promyelocytic leukaemia protein (PML) gene is involved in the

t(15;17) chromosomal translocation of acute promyelocytic leukaemia (APL). It encodes the PML protein, which localises to PML nuclear bodies and functions as a growth/tumour suppressor. We previously identified that PML plays an important role in the regulation of NPCs in the developing neocortex of the mouse. One obvious question is how NPCs in adult neurogenic niches respond to PML loss, in particular those associated with neoplastic transformation. Here, we show that loss of PML leads to alterations in NPC proliferation and cell fate decisions in the adult subventricular zone. We then performed an extensive analysis of PML expression and function in human GBM. This analysis has revealed a totally unexpected role of PML in GBM and in particular in the regulation of cell fate in GBM neural stem cells. Overall, our findings reveal key roles of PML in both normal and neoplastic NPCs, and may have important implications for the understanding of brain cancer pathogenesis.

The Autophagic Response as a Putative Determinant for Disease Preventive or Therapeutic Effects of n-3 Polyunsaturated Fatty Acids

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Epidemiologic studies have suggested an inverse correlation between dietary intake of marine lipids (n-3 polyunsaturated fatty acids, PUFAs) and the risk of different types of cancer, neurodegenerative diseases and heart and circulatory disturbances. In addition, several cancer cell lines have been found sensitive and die when exposed to PUFAs both in cell cultures and when implanted in mice. A firm understanding of the disease preventive mechanism(s) mobilized by PUFAs is not established. Also, if the putative preventive and therapeutic mechanisms are related or independent is incompletely understood.
Using genome wide expression analyses we find a number of autophagy genes among the primary response genes to PUFAs. However, in cancer cells sensitive for PUFAs, we find a low level of basal autophagy and that the transcriptional activation of autophagy not results in a substantial increase in the process. On the other hand, cancer cell lines insensitive for PUFAs display a higher level of autophagy both in the absence and presence of marine lipids. Accordingly, we find embryonic derived fibroblasts from autophagy deficient mice to be significantly more sensitive for PUFAs compared to wild type cells.
These results suggest autophagy as a potential disease preventive process mobilized by PUFAs in normal cells. The results also imply a possible therapeutic effect of PUFAs against cancer cells with reduced autophagy. To further investigate possible disease preventive or therapeutic effects of PUFAs we will need biomarkers that can report on status and changes of autophagy in clinical samples. Attempts to monitor regulation of autophagy in clinical samples will be presented and discussed.