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Short Commentary Open Access

The Role of N-Terminal Acetyltransferase NAA30 in Glioblastoma-Initiating Cells

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Glioblastoma (GBM) is one of the deadliest human cancers with overall survival of less than a year. Standard therapy against GBM consists of combined surgery, radiation- and chemo-therapy. However, GBMs remain aggressive and the cure is never achieved. It has been suggested that the presence of highly invasive stem-like cells, contained within these tumors, is responsible for resistance to irradiation and chemotherapy (for overview of the literature see Lathia et al.) [1]. These cells are considered to be important for retaining the GBM properties and are often referred to as glioblastoma-initiating cells (GICs) (also called glioblastoma stem cells, GSCs). Because of their role in tumor initiation and maintenance, these cells are the obvious choice for therapeutic targeting.

We recently reported that the gene *NAA30*, encoding a N-terminal acetyltransferase is up-regulated in GBMs and that it regulates stemness and proliferation of GICs [2]. *NAA30* gene (or its yeast homologue *MAK3*) was first described through its mutation in yeast in 1976 [3] but its function as N-terminal acetyltransferase was not revealed until the early nineties [4]. N-terminal acetyltransferases (NATs) comprise a group of evolutionary conserved enzymes present in all eukaryotes from yeast to humans. Human NATs are organized in six complexes (NatA-NatF) whose role is in transferring the acetyl group from acetyl-coenzyme A to the N-terminal amino acid of the nascent protein [5]. N-terminal acetylation is involved in regulation of cellular processes such as protein degradation, targeting of proteins to organelles and formation of protein complexes. NATs are up-regulated in various malignancies such as hepatocellular and cervical carcinomas, colorectal cancers, glioblastomas and cancers of thyroid, lung, breast and bladder. Several studies showed that the components of the NAT complexes represent potential therapeutic targets for the treatment of cancer.

NAA30 is a catalytic subunit of the NatC complex. In GIC cultures featuring knockdown of *NAA30* gene we observed significant reduction of growth and proliferation [2]. Sphere forming ability, that reflects the number of stem-like cells, and is an indicator of tumor aggressiveness, was also reduced. Furthermore, the SCID mice transplanted with *NAA30* depleted GICs survived significantly longer than controls. Our study also showed that the human *NAA30* is represented with transcripts that contain 3'UTR regions of variable length. The expression of the distal end of 3'UTR was strongly down-regulated in GBM and GICs but not in the normal brain tissue or the neural stem cells from the normal adult human brain. Moreover, the decreased expression of the distal 3'UTR region correlated with a shorter survival of glioma patients. Another study reported that shortening of 3'UTRs correlated with poor patient survival in breast and lung cancer [6]. Interestingly, regulatory functions of the 3'UTR of the yeast *NAA30* homologue *MAK3* were reported already in 1992 [4]. The authors of the study in yeast implied that the role of the 3'UTR (in *MAK3* transcript) could be in transport of mRNA from nucleus to the cytoplasm and in ensuring proper translation [4]. The presence of miRNA in the 3'UTR was also anticipated [4]. We came to the same conclusion in our study in GICs [2].

Our study also revealed that *NAA30* regulates hypoxia response [2]. In GIC cultures featuring *NAA30* knockdown we detected decreased levels of HIF1α protein as well as decreased levels of p-MTOR (Ser2448) [2]. Knockdown of *NAA30* further influenced the p53 pathway, expression of ribosomal proteins and the expression of glial fibrillary acidic protein (GFAP). Another study showed that the knockdown of *NAA30* and the whole NatC complex in HeLa cells caused p53-dependent apoptosis and aberrant localization of ARL8B [7].

It is interesting that the research that was conducted through the seventies and nineties in yeast could be so relevant for understanding the biology of cancer. This emphasizes the role of basic research, without which the design of new therapies for patient treatment would be impossible.

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