Matrix glycans as multifunctional pathogenesis factors and therapeutic targets in cancer

Rapports

Informations projet

GLYCANC

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Periodic Reporting for period 2 - GLYCANC (Matrix glycans as multifunctional pathogenesis factors and therapeutic targets in cancer)

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Résumé du contexte et des objectifs généraux du projet

Cancer is a leading cause of mortality within the aging European population and implies high costs for the general public. Eradication of cancer proves to be difficult, as disease mechanisms are complex. Not only molecular changes within the tumor, but also in the extracellular environment surrounding the tumor are important for the disease. This environment includes blood vessels and immune cells, which are hijacked and reprogrammed by the tumor to facilitate its growth. Recent research demonstrated that sugars called glycosaminoglycans (GAGs) and glycoproteins called proteoglycans (PGs) influence tumor growth and metastasis. As the role of these sugars in cancer has only been recently discovered, PG and GAG-based drugs will differ from existing drugs and may help to overcome resistance to therapy. We hypothesize that these drugs will stop multiple processes of cancer development and will therefore be superior to existing therapeutics. PGs and GAGs are currently under-investigated as their analysis is technically challenging. However, GLYCANC forms a team of specialists within the glycobiology field well-qualified to address this important research question. The understanding of the way these sugars work, and how this knowledge can be used for drug development was a major objective of GLYCANC. Other objectives were the development of new analytical technologies called spectroscopy and atomic force microscopy (AFM) to understand why they help tumor cells to grow and metastasis. Moreover, we wanted to understand new ways by which PGs and GAGs are regulated in a different way in cancer and normal cells by a process called epigenetics. With exchanges of university- and industry-based researchers between Europe, South America and Asia, GLYCANC has provided excellent interdisciplinary training for young scientists which became specialists in an upcoming and important research field. GLYCANC promoted the exchange of technologies and scientific ideas between industry and universities, leading to a more efficient research and a better qualification of all participants. As documented in 25 scientific publications so far, GLYCANC has substantially enhanced our understanding how proteoglycans regulate all relevant steps of tumor progression, has resulted in the development of new analytical

techniques, and has resulted in the development of new glycoscience-based therapeutic approaches. As new proteoglycan targeting drugs have been successfully evaluated by the GLYCANC consortium in preclinical studies, the development of more efficient treatments can now proceed more rapidly, with considerable benefits for affected patients and society.

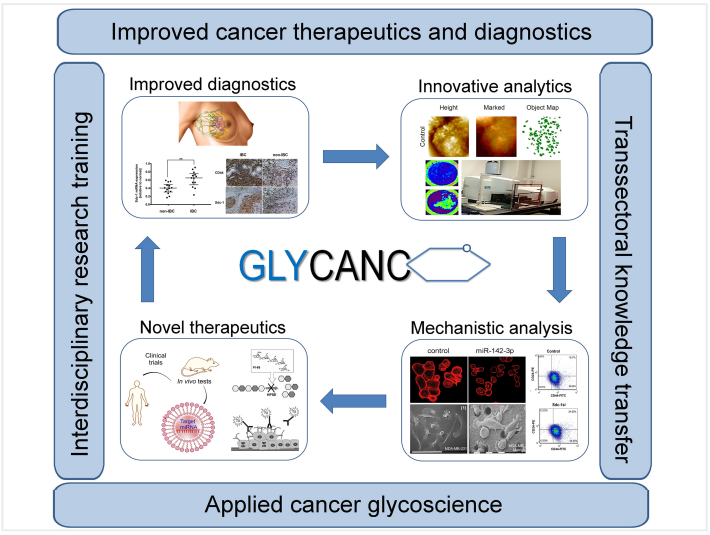
Travail effectué depuis le début du projet jusqu'à la fin de la période considérée dans le rapport et principaux résultats atteints jusqu'à présent

We successfully developed new analytical methods by applying biophysical technologies called RAMAN spectroscopy and FITR analysis. These technologies have not yet been used extensively in sugar analytics before, and we have developed new protocols for their application: Our methods can distinguish normal tissue from tumor tissue with high reproducibility, and distinguish aggressive from less aggressive tumor cells based on differences in sugar structures. These findings provide clinicians with new tools for patient diagnostics. Importantly, our label-free sample preparation is much easier applicable than existing technologies. We successfully applied AFM, detecting tumor cell structures a million times smaller than a millimeter, to distinguish aggressive from less aggressive tumor cells. We also showed that small nucleic acids called microRNAs are regulated by hormones and determine how PGs and GAGs are made in different amounts and with a different structure in tumor cells compared to healthy cells. Importantly, tumor cells become less aggressive when treated with microRNA-based drugs. Moreover, we successfully analysed how PGs and GAGs contribute to all key steps of tumorigenesis and tumor progression. As particular highlights, we demonstrated an impact on so-called cancer stem cells, a cell type particularly resistant to chemo- and radiotherapy, which may represent a promising future therapeutic approach. Moreover, the presence or absence of PGs and GAGs has an influence on how good conventional anticancer therapeutics work. This knowledge can be used to improve conventional therapies. For example, we showed that inhibition of the enzyme heparanase stopped experimental brain tumors from growing. Furthermore, manipulation of the PG Syndecan-1 in tumor cells and their environment changed their resistance to chemotherapy and radiation therapy. We published the project results in 25 scientific publications so far, and presented them to the scientific community at several international conferences. Moreover, we successfully trained 32 young researchers in the field of cancer glycobiology and biotechnology.

Progrès au-delà de l'état des connaissances et impact potentiel prévu (y compris l'impact socio-économique et les conséquences sociétales plus larges du projet jusqu'à présent)

Several aspects of GLYCANC reach beyond the current state of the art: Glycoscience is an under-investigated area of cancer research, and the mechanistic contributions we made to understand how specific GAG structural patterns and misexpression of PGs and GAGs contribute to tumor progression and metastasis is an important addition to the field. Several innovative techniques and subtopics with high commercialization potential for analytics, diagnostics and therapeutics resulted from GLYCANC. The application of quantitative AFM, RAMAN glycoanalytics, available as

standardized protocols, cancer stem cell analysis and endocrine regulation of microRNAs targeting PGs and GAGs are highly novel aspects, which have been successfully evaluated in several cell models, in in vivo models of cancer, and in patient-derived samples. Epigenetic regulation of PG and GAG (mis)expression in cancer has been evaluated in mechanistic detail providing sufficient data in preclinical models to assess their potential for drug development. Overall our data strongly confirm that PGs and GAGs modulate all steps of tumor progression. Preclinical data for novel therapeutic approaches, including miRNA drugs, drugs inhibiting GAG-processing enzymes, and glycan-based inhibitors of cancer stem cells have been generated, which are laid down in 25 publications of our consortium, and were presented at major scientific conferences, notably the GRC and International conferences for proteoglycans, several FEBS lecture courses, and Matrix Biology Europe. Moreover, our research was disseminated via social media, open university days and press notices. We have strengthened the European research area by establishing a novel and strong network of European and non-European researchers benefitting considerably from the exchange of expertise and resources, thus strengthening their position as opinion leaders. Moreover, we have strengthened cooperation between academic and non-academic partners for their mutual benefit, and exploited the translational potential of this project in the fields of quantitative AFM, spectroscopy-based glycoanalytics, as well as miRNA- and PG/GAG-based anticancer therapeutics. By this way, the impact on society is high, as young European researchers received excellent interdisciplinary training in an important and specialized research area for which a high demand exists both in the academic community and in industry. By closing important knowledge gaps in the area of carbohydrate-related cancer research, GLYCANC made a major contribution to the preclinical development of more efficient anti-cancer drugs and diagnostics.



Overview of the GLYCANC project.

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