Potențiali biomarkeri proteici cu utilitate în diagnosticul colangiocarcinomului intrahepatic

Project name: Potential proteomic signature based biomarker for intrahepatic cholangiocarcinoma diagnosis

Acronym: PROTiCC

Project ID: PN-III-P1-1.1-PD2019-0852

Project Team

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Budget: 246.950,00 RON (2 years)

Abstract

Intrahepatic cholangiocarcinoma (iCCA) is the second most common subtype of liver cancer, fourth leading cause of cancer related deaths worldwide. Worryingly, 2019 statistics show that iCCA incidence rates are raising faster than for any other cancer. With a dismal 5-year relative survival rate of solely 17%, iCCA has a hopeless prognosis explained by its refractory nature and late diagnosis, hindered by its asymptomatic makeup in the early phase. Currently, iCCA is diagnosed by combining clinical, radiological and nonspecific markers. Even thought surgery is a potentially curative option, only few patients can benefit, recurrence and survival rates being discouraging. As such, iCCA represents a global health problem and considerable efforts need to be made towards improving patients overall survival.

One trustworthy option is its early diagnosis by an accurate follow-up of the precursor lesions. Thus, iCCA could be timely detected and successfully treated. The current gold standard for a conclusive diagnosis of liver malignancies is the tumor biopsy. Dismally, its sensitivity is only 74.6% and in patients with typical imagistic criteria of hepatocellular carcinoma, the histological diagnosis is iCCA in 12.5% of the patients. Yet, biopsy is not indicated in the majority of the cases because of the advanced stage and concomitant risks. As such, there is an urgent medical need for the development of an accurate diagnostic tool for iCCA. One encouraging option for iCCA patients could be a proteomic based biomarker signature, currently in the light of personalized medicine studies.

Objective

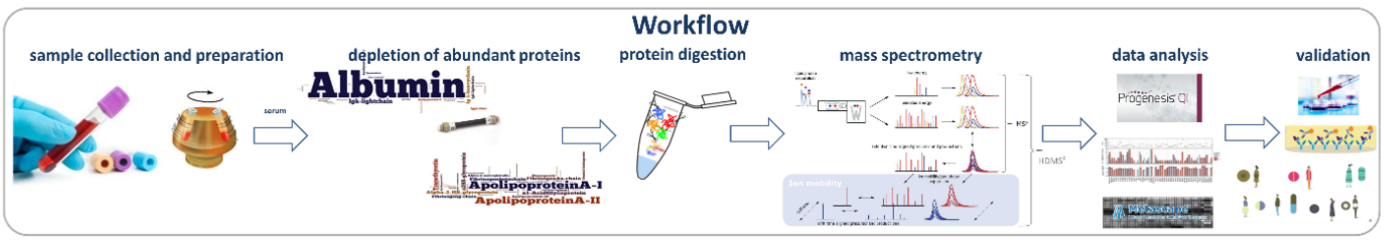
The major objective of the present project proposal is to explore the serum proteome of iCCA patients in comparison to primary sclerosing cholangitis, chronic hepatitis, liver cirrhosis, hepatocellular carcinoma and healthy controls and to find proteomics based biomarker signatures of iCCA towards clinical utility by employing state of the art mass spectrometry based techniques.

Specific objectives

O1. Characterization of the serum proteome of iCCA patients in comparison to primary sclerosing cholangitis, chronic hepatitis, liver cirrhosis, hepatocellular carcinoma and healthy controls by a state of the art paramagnetic bead-based sample preparation method and lable free nanoLC- ion mobility UDMSE mass spectrometry based approach.

O2. Identification of differently abundant protein panels as potential biomarkers among the analyzed groups that could aid diagnosis of iCCA, as well as differential diagnosis between the groups.

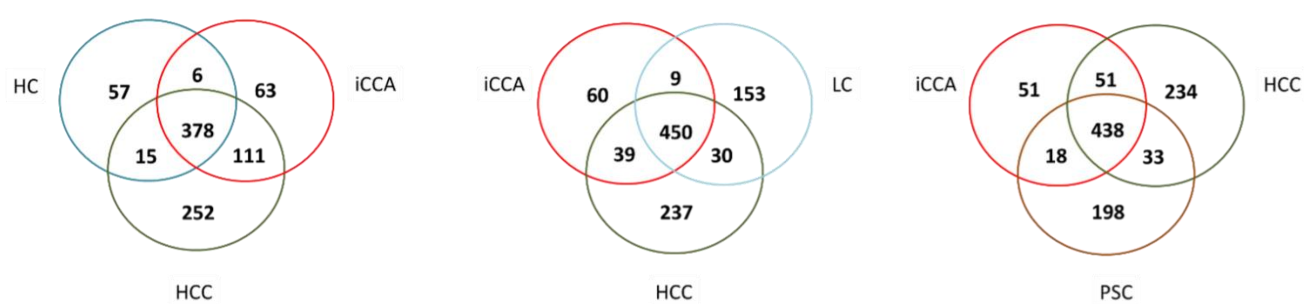
O3. Validation of the potential biomarkers by using a complementary approach in an independent cohort of patients.



Results:

Complete serum protein profiles of patients with intrahepatic cholangiocarcinoma, primary sclerosing cholangitis, chronic hepatitis, liver cirrhosis and healthy controls by state of the art mass spectrometry proteomic techniques and unique protein panels with potential biomarker role towards clinical use for the intrahepatic cholangiocarcinoma patient.

Overview on the common and unique proteins among the studied cohorts



Top 25 most abundant proteins identified with the median relative abundance among the groups

	UniPROT ID and protein name	iCCA	HCC	PSC	LC	HC
1	P01023 Alpha-2-macroglobulin	6165665.50	8650203.55	4623285.88	7656881.10	3519990.76
2	P01024 Complement C3	6159093.50	4168365.10	3666719.52	4545395.33	3051754.73
3	P04114 Apolipoprotein B-100	2811738.82	2157772.74	1756740.35	1958090.12	1353254.72
4	P02647 Apolipoprotein A-I	2729245.50	3220102.44	2900735.11	3663722.13	3012496.24
5	P02790 Hemopexin	1778639.59	1572643.24	1409789.31	1666341.42	1436307.61
6	P00450 Ceruloplasmin	1700753.93	1551972.36	1092141.85	1484139.56	861967.01
7	P02774 Vitamin D-binding protein	1005801.21	897212.95	651713.54	909228.03	635502.67
8	P02652 Apolipoprotein A-II	918971.89	1255880.49	899092.70	1337398.06	786014.33
9	P02768 Albumin	690460.13	699425.08	1767236.51	860187.96	1764174.88
10	P08603 Complement factor H	673270.18	645258.09	430872.65	581285.90	381868.04
11	P02763 Alpha-1-acid glycoprotein 1	669022.81	449010.76	396582.65	543698.25	404201.49
12	P01011 Alpha-1-antichymotrypsin	637574.36	375730.37	260940.36	507980.46	185085.44
13	Q14624 Inter-alpha-trypsin inhibitor H4	621909.98	440122.48	396086.93	520279.00	293582.46
14	P04217 Alpha-1B-glycoprotein	611272.45	550895.93	432518.79	522881.18	336854.93
15	P02765 Alpha-2-HS-glycoprotein	461799.62	627306.63	544865.02	556572.12	275805.46
16	P00751 Complement factor B	452369.49	308265.48	278940.11	372997.05	220596.12
17	P19823 Inter-alpha-trypsin H2	449079.11	362004.14	308447.90	374056.49	292952.43
18	P02766 Transthyretin	433616.05	413906.56	396772.55	430586.42	551955.26
19	P02749 Beta-2-glycoprotein 1	417289.98	457173.60	283350.02	486564.56	234986.88
20	P04004 Vitronectin	401543.77	294686.56	303202.67	331954.62	303605.44
21	P01008 Antithrombin-III	389114.16	345101.76	314501.34	346998.99	326024.46
22	P00747 Plasminogen	366382.16	372181.11	294256.56	343558.18	357857.51
23	P69905 Hemoglobin subunit alpha	365478.00	81013.34	237424.33	31948.37	9429.37
24	P01031 Complement C5	296683.69	238717.25	156014.97	237122.72	125959.75
25	P01019 Angiotensinogen	280354.32	237316.24	149666.29	291377.88	198264.99

Conclusions

PROTiCC is the first project to exploit the serum proteome of patients diagnosed with intrahepatic cholangiocarcinoma in comparison with primary sclerosing cholangitis, liver cirrhosis, hepatocellular carcinoma, and healthy controls towards proteome biomarker discovery for clinical use. Five groups of participants were included and by using high throughput mass spectrometry complete serum profiles were identified. Common and unique proteins were highlighted and subjected to validation of their potential role of diagnostic biomarkers for patients with intrahepatic cholangiocarcinoma.

Impact

Enthusiastically, the project has a great potential to impact both the social and the economical environment through the contributions in the clinical field. Firstly, the results will catalyze future collaborations with research Consortium, like the European Network for the Study of Cholangiocarcinoma (ENS-CCA), or with Biotechnology or pharmaceutical companies, accelerating the goal of precision medicine. Furthermore, the results of the present project proposal will support the development of a biomarker based diagnostic tools. Until mass spectrometry-based diagnostic in the clinics or diagnostic centers a diagnostic tool based on an ELISA kit could be easily developed for the new biomarker panel. By the clinical utilization of a serum signature-based biomarker towards early diagnosis of iCCA the project takes a step forward to greatly enable adequate clinical management of the patient, improve iCCA patient clinical outcome and extremely important, patient survival, a very actual global health problem.

Project outputs

(1) Conferences in the project field

• Human Proteome Organization - HUPO ReCONNECT 2021 – 15-19 November 2021, on-line

• Proteomic Forum 2022 – 3-7 April 2022, Leipzig, Germany

• Poster presentation:

- Title: Serum proteome profiling of intrahepatic cholangiocarcinoma towards diagnostic biomarker identification
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(2) Scientific papers

- Mocan, L. P., Ilieș, M., Melincovici, C. S., Spârchez, M., Crăciun, R., Nenu, I., Horhat, A., Tefas, C., Spârchez, Z., Iuga, C. A., Mocan, T., & Mihu, C. M. (2022). Novel approaches in search for biomarkers of cholangiocarcinoma. World Journal of Gastroenterology, 28(15), 1508–1525. https://doi.org/10.3748/wjg.v28.i15.1508

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