Predictive metabolomics signature of relapse in metastasic colorectal cancer

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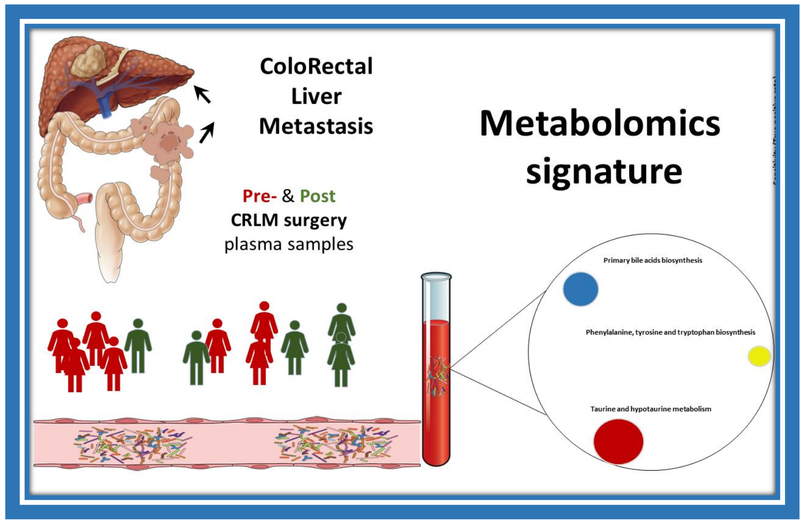
Colorectal liver metastasis (CRLM) is the main cause of colorectal cancer (CRC) deaths. Understanding the molecular profile of each CRC can help to predict its prognosis and response diversity among patients. The goal of this work was to identify a precise metabolomics signature of disease relapse in CRLM patients after metastasectomy. A pilot metabolomics study was conducted at the University Hospital of Jaén using plasma samples from 39 patients with CRLM before and after metastasectomy. Paired samples were analysed using reverse phase (RP) and hydrophilic interaction liquid chromatography (HILIC) coupled to high-resolution mass spectrometry (HRMS).



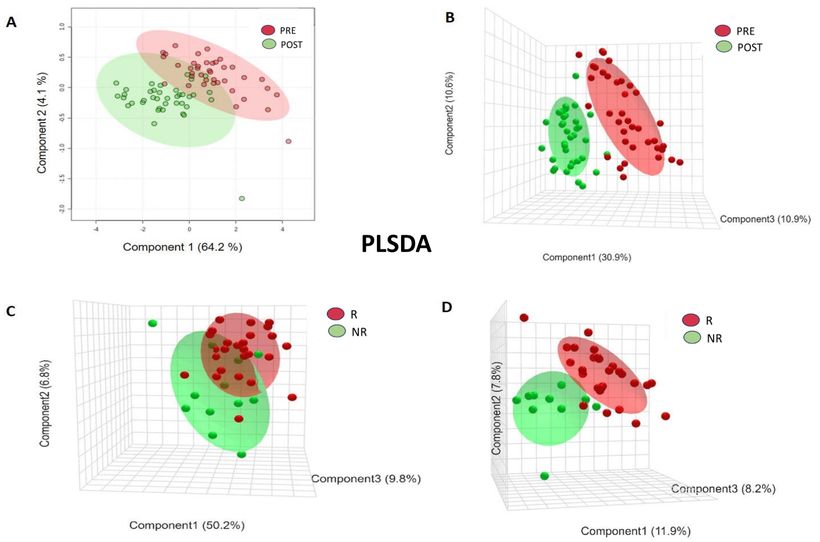
Conclusions

This study shows that easily detectable circulating metabolites in plasma samples might be used to predict disease recurrence and have a prognostic value for CRLM patients undergoing surgery.

Our analysis identifies a model based on 12 metabolites that enables a precise stratification of disease progression and, consequently, a personalized follow-up in the clinical setting.

LCHRMS ANALYSIS

The molecular profiling of recurrence 2 years post metastasectomy was carried out by univariate and multivariate statistical strategies



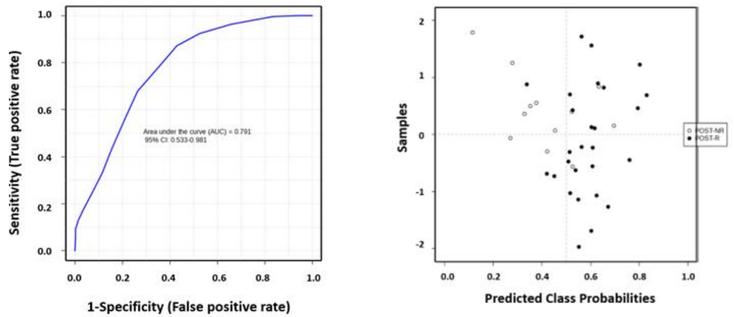
Supervised PLS-DA score plots shows the discrimination between pre- and post-surgery plasma samples (red and green dots respectively), using two components in RPLC ESI + (**A**) and three components for HILIC ESI – (**B**) methods. PLS-DA score plots illustrate the differentiation in post-surgery samples of recurrent (red dots, R) and non-recurrent (green dots, NR) patients with CRLM, by using three components in RPLC ESI + (**C**) and HILIC ESI – (**D**) analyses.

Tentative identification of the candidate biomarkers of CRLM recurrence post-surgery detected by two LC-HRMS strategies

LC-HRMS	m/z	R.T (min)	FC (RtoNR)	VIP	Molecular Formula	Putative ID	Adduct	Mass error (ppm)
HILIC ESI -	**124.0067***	3.8	0.751	1.988	C2H7NO3S	Taurine	M-H	3.3
	135.0295*	2.85	0.652	1.442	C5H4N4O	Hypoxanthine	M-H	-4.7
	193.0358*	3.87	0.549	1.447	C6H10O7	Galacturonic acid	M-H	1.7
	307.1507	5.21	1.434	1.515	C12H24N2O7	Fructose-Lysine	M-H	3.0
	336.0895	3.91	0.484	1.059	C6H12O7	D-Gluconic-related acid	M-H	0.0
	353.1582	1.27	4.047	1.323	C18H26O7	Propofol glucuronide	M-H	-2.7
	369.1727	1.65	1.428	1.593	C19H30O5S	Androsterone sulfate	M-H	-2.3
	452.2789*	1.82	0.743	2.145	C21H44NO7P	LysoPE(16:0)	M-H	-3.2
	464.299	1.34	2.175	1.837	C26H43NO6	Glicocholic acid	M-H	0.9
	498.2887*	2.54	1.296	1.296	C26H45NO6S	Taurochenodeoxycholic acid	M-H	2.6
	514.2818*	2.97	1.837	1.837	C26H45NO7S	Taurocholic acid	M-H	-2.9
	583.2544*	1.18	1.36	1.36	C33H36N4O6	Bilirubin	M-H	-1.7
RPLC ESI +	**454.2918***	11.2	0.735	1.571	C21H44NO7P	LysoPE(16:0)	M+H	-2.2
	478.2925*	10.6	0.736	1.511	C23H44NO7P	LysoPE(18:2)	M+H	-0.7
	480.3439*	12.2	0.781	1.682	C24H50NO6P	LysoPC(P-16:0)	M+H	-2.0
	482.3211*	13.2	0.773	1.452	C23H48NO7P	LysoPE(18:0)	M+H	-4.4
	512.3348*	10	0.773	1.632	C24H50NO8P	Unknown LysoPC	M+H	1.0
	526.2912*	10.6	0.768	1.407	C27H44NO7P	LysoPE(22:6)	M+H	1.3
	548.2693		0.757	1.486			M+Na	-1.3
	564.3056	10	0.725	1.054	C28H48NO7P	LysoPC(20:5)	M+Na	-0.8

m/z: mass/charge ratio; R.T: retention time; FC: fold change > 1.3 indicates that the average normalized peak area ratio in post-surgery samples of recurrent patients with CRLM (R) is larger than that in non-recurrent patients (NR); VIP: variable of importance in projection; ID: identification; *: **candidates selected for the diagnostic model**; LysoPE: lysophosphatidylethanolamines; LysoPC: lysophosphatidylcholines.

Biomarker evaluation: ROC Curves



Multivariate ROC curve plots from the average of 100 cross-validations for the model combination of the thirteen metabolomics features identified in both analytical strategies (**A**). Classification using the average of predicted group probabilities of each sample provided a confusion matrix where 23 recurrent patients were correctly classified and 4 misclassified; 8 non-recurrent patients were correctly classified and 4 misclassified (**B**).

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