Søknadsinformasjon

Utlysning	Nordic Cancer Union Research Grant, 2014
Søknad	Exploring immune cell properties of cancer cells as an early sign of metastasis in Swedish and Finnish breast cancer patients
Søknadsid	155417
Innsendt av	Jonas Fuxe

Oppgave: Progress report

Tilordnet	Jonas Fuxe
Status	Arkivert
Opprettet	04.02.2016

RAPPORT

Briefly describe the project in a language understandable to non-scientists

Metastatic spread of cancer cells to vital organs is the major cause of death in breast cancer and many other forms of cancer. A clinical problem is that it is difficult to predict which patients that eventually may be at risk of developing metastatic disease. Few tools exist to detect early signs of metastasis. Inflammation is linked to cancer progression into metastatic disease, but the mechanisms are not fully understood. Others and we have found that certain inflammatory factors, such as TGF-beta, may switch on a developmental program in cancer cells. This program is termed epithelial-mesenchymal transition (EMT), and promotes the invasive and metastatic properties of breast cancer cells. Based on this, we initiated a research program, which was funded by the Nordic Cancer Union, to explore the properties of EMT cells as novel markers of early invasion metastasis in breast cancer.

Summarize the major findings of the project

1. Gene profiling experiments lead to the identification of a cluster of genes, which were induced in tumor cells induced to undergo EMT by TGF-beta, and are normally expressed in monocyte-derived macrophages, mast cells, and myeloid dendritic cells, but less in other types of immune cells. Further studies revealed that this monocyte/macrophage gene cluster was enriched in human breast cancer cell lines displaying a Basal B profile, and in human breast tumors with undifferentiated (ER-/PR-) characteristics. The results identify a monocyte/macrophage gene cluster, which may play a role in breast cancer cell dissemination and metastasis.

2. We found that tumor cells undergoing EMT in response to TGF-beta become activated for targeted migration through the lymphatic system, similar to dendritic cells (DCs) during inflammation. Such cells preferentially migrated toward lymphatic vessels compared with blood vessels, both in vivo and in 3D cultures. A mechanism of this targeted migration was traced to the capacity of TGF-1 to promote CCR7/CCL21-mediated crosstalk between tumor cells and lymphatic endothelial cells. On one hand, TGF-1 promoted CCR7 expression in EMT cells through p38 MAP kinase-mediated activation of the JunB transcription factor. Blockade of CCR7, or treatment with a p38 MAP kinase inhibitor, reduced lymphatic dissemination of EMT cells in syngeneic mice. On the other hand, TGF-1 promoted CCL21 expression in lymphatic endothelial cells. CCL21 acted in a paracrine fashion to mediate chemotactic migration of EMT cells toward lymphatic endothelial cells. The results identify TGF-1-induced EMT as a mechanism, which activates tumor cells for targeted, DC-like migration through the lymphatic system. Furthermore, it suggests that p38 MAP kinase inhibition may be a useful strategy to inhibit EMT and lymphogenic spread of tumor cells.

3. Recent unpublished results indicate that some of the identified EMT regulated genes might be prognostic markers for survival in breast cancer patients. Ongoing studies aim to identify the most promising candidates and study their expression by immunostaining of tumor specimens from surgical samples of breast cancer.

Describe how the project has increased our knowledge of the prevention, cause and/or cure for cancer

Others and we have found that EMT, which is a latent developmental process, can be re-activated in tumors and provide cancer cells with migratory and pro-metastatic properties. Thus, signs of EMT activation in tumors may represent an early sign of metastasis. However, present markers of EMT do not distinguish between cancer cells that have undergone EMT and stromal cells, such as fibroblasts. Thus, there is a need to identify novel markers that could be used to detect EMT cells in primary tumors and in the circulation of patients with breast cancer.

The studies outlined in this program have provided novel insights into the properties of breast cancer cells undergoing EMT in response to TGF-beta. The results identified a monocyte/macrophage gene cluster, which may play a role in breast cancer cell dissemination and metastasis. The results also identified TGF-1-induced EMT as a mechanism, which activates tumor cells for targeted, DC-like migration through the lymphatic system. Furthermore, it suggests that p38 MAP kinase inhibition may be a useful strategy to inhibit EMT and lymphogenic spread of tumor cells. Ongoing studies are expected to result in the identification of novel markers of cancer metastasis.

Outline how Nordic cooperation has added value to this project

The funding of this research program by the Nordic Cancer Union has been tremendously important for its progress. It allowed us to explore our initial results and aim for a more comprehensive analysis of the possibility to use EMT markers to detect pro-metastatic cancer cells in breast cancer tissues. We are currently trying to screen our novel EMT markers for their expression in various forms of human breast cancer. The goal is to identify a small set of genes/proteins that can be used as novel markers of metastatic behavior. We look forward to future collaborations with the Nordic Cancer Union.

List the publications resulting from the NCU research grant

Author(s), title, journal and edition	PMID (8 digits, only if possible)
Johansson J, Tabor V, Wikell A, Jalkanen S, Fuxe J. TGF-1-Induced Epithelial-Mesenchymal Transition Promotes Monocyte/Macrophage Properties in Breast Cancer Cells. Front Oncol. 2015 Jan 26;5:3	25674539
Pang MF, Georgoudaki AM, Lambut L, Johansson J, Tabor V, Hagikura K, Jin Y, Jansson M, Alexander JS, Nelson CM, Jakobsson L, Betsholtz C, Sund M, Karlsson MC, Fuxe J. TGF-1-induced EMT promotes targeted migration of breast cancer cells through the lymphatic system by the activation of CCR7/CCL21-mediated chemotaxis. Oncogene. 2016 Feb 11;35(6):748-60	25961925

Brief overview of expenditures for last year 1 vedlegg (Ekonomisk rapport J. Fuxe NCU.pdf)

Redovisning NCU Dnr 4-3128/2014

3522	Bidrag från länder utanför EU	C27107113	85NCU	-462 200,00	-462 200,00
Lön					
4011	Löner och arvoden fast anställda	C27107113		137 597,00	
40118	Inst interna löner	C27107113		22 073,18	
4060	Soc.avg. löner och arvoden	C27107113		68 333,87	228 004,05
Stipendier					
7931	Lämnade bidrag till enskilda personer	C27107113		40 000,00	40 000,00
Resor					
4321	Skattefria traktamenten, Sverige	C27107113		363,00	
4322	Skattepliktiga traktamenten, Sverige	C27107113		236,30	
4323	Skattefria traktamenten, utlandet	C27107113		1 324,80	
5513	Taxi inrikes	C27107113		603,77	
5515	Övriga resekostnader inrikes	C27107113		448,00	
5522	Flyg utrikes	C27107113		22 505,00	
5524	Hyrbilar utrikes	C27107113		3 799,60	29 280,47
Drift					
40218	Inst interna övriga tjänster	C27107113		19 440,00	
5223	Reservdelar	C27107113		1 317,00	
5612	Korttidsinvesteringar datorer och datautrustning	C27107113		5 372,75	
5627	Kontorsmateriel	C27107113		556,00	
5642	Kemikaliekits/Molekylärbiologiska kits	C27107113		17 813,04	
5651	Biologiska ämnen	C27107113		22 244,18	
5654	Celler, bakterier och vävnadskulturer	C27107113		215,90	
56619	Djur (KI-intern faktura)	C27107113		150,43	
5672	Cellodlings plastartiklar	C27107113		10 020,71	
5673	Övriga laboratorieplastartiklar	C27107113		4 672,00	
5693	Förbrukningsmateriel	C27107113		238,80	82 040,81
Övriga kostnader					
4360	Soc.avg. kostnadsersättningar och naturaförmåner	C27107113		116,93	
49408	Projektavslut	C27107113		-6 042,37	
4961	Personalrepresentation	C27107113		1 959,99	
4969	Övriga personalkostnader	C27107113		2 282,60	
5221	Reparationer av maskiner och teknisk apparatur	C27107113		388,00	
5222	Service- och underhållsavtal	C27107113		2 535,55	
5531	Extern representation	C27107113		2 961,40	
5761	Korttidshyra/leasing, maskiner, inventarier mm	C27107113		3 808,00	
5771	Frakter och transporttjänster	C27107113		242,50	
5922	Dröjsmålsräntor utomstatliga	C27107113		209,00	8 461,60
OH					
49968	Gemensamma kostnader institution	C27107113		28 924,53	
49978	Gemensamma kostnader fakultet	C27107113		5 676,81	
49988	Gemensamma kostnader universitet	C27107113		39 811,73	74 413,07
					462 200,00
				SALDO	0,00