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Mini-Review

Role of co-expression of LGR5 and NANOG in the development of aggressive human cancer

Abraham Amsterdam[1,*], Dror Ofir[2] and Tal Rakler[1]

[1]Department of Molecular Cell Biology; [2]Biological Services, The Weizmann Institute of Science, Rehovot 76100, Israel.

ABSTRACT

The potential role of the co-expression of NANOG, an embryonic pluripotent gene, and LGR5, a stem cell marker, in pancreatic ductal adenocarcinoma (PDAC) and in human ovarian cancer, is discussed in this mini-review.

KEYWORDS: LGR5, NANOG, PDAC, cancer lethality, cell death programing.

INTRODUCTION

It is believed that in human cancer the development of the bulk of cancerous tissue while the disease is in process is homogeneous and continuous. Such a process can be seen in detail, for example, in the development of P53 and pERK expression [1]. It was reported through all types of tumors observed microscopically. This view was believed to be true until recently when it was discovered by Amsterdam *et al*. [1] that this may not be the case when phosphorylated LGR5 and NANOG interact within the tumor which will make the cancer much more aggressive, probably by accelerating the cancer cell growth, which may lead to rapid death of the patient, possibly associated with change of the shape and function of the cancer cells responsible for this phenomena. In the current review we shall discuss the impact of such a view to our understanding of the mechanism of rapid death in human cancer. It may raise the challenge to study how to control this phenomenon in order to reduce cancer-related death.

*Corresponding author
Abraham.amsterdam@weizmann.ac.il

The experimental approach

In Darwin's time, people were excited about the selective evolution of humans and other creatures on the globe. However, when it was revealed very recently that there is also an existing mechanism of programmed cell death by proteolysis of the living organism [2-6], it was a 180-degree turn in our understanding of evolution. It was not until 2011 when a possible mechanism for the precise point of the onset of malignancy of carcinogenic cells, upon co-expression of the pluripotent gene NANOG [7] and the LGR5 stem cell marker [2] that identifies the starting point of the termination of malignant tissue, was discovered. Moreover, it seems that the signal came at the proper time in the pancreas and in the ovary, when the ovarian role of reproduction terminates, and in the pancreas when the process of sugar cleavage and protein degradation that are essential for nutrition terminates. [3], It happens to be that this cluster of papers was published during a short period of time, yet it still raised the idea that there is a very precise programming, for termination of life, which we should explore in the future. Of course, this is an over-simplification of the story and much more has to be added to it.

Since our last paper, new information was accumulated, which fits this hypothesis. For example in 2018, LGR5, CD44 and EpCAM cells

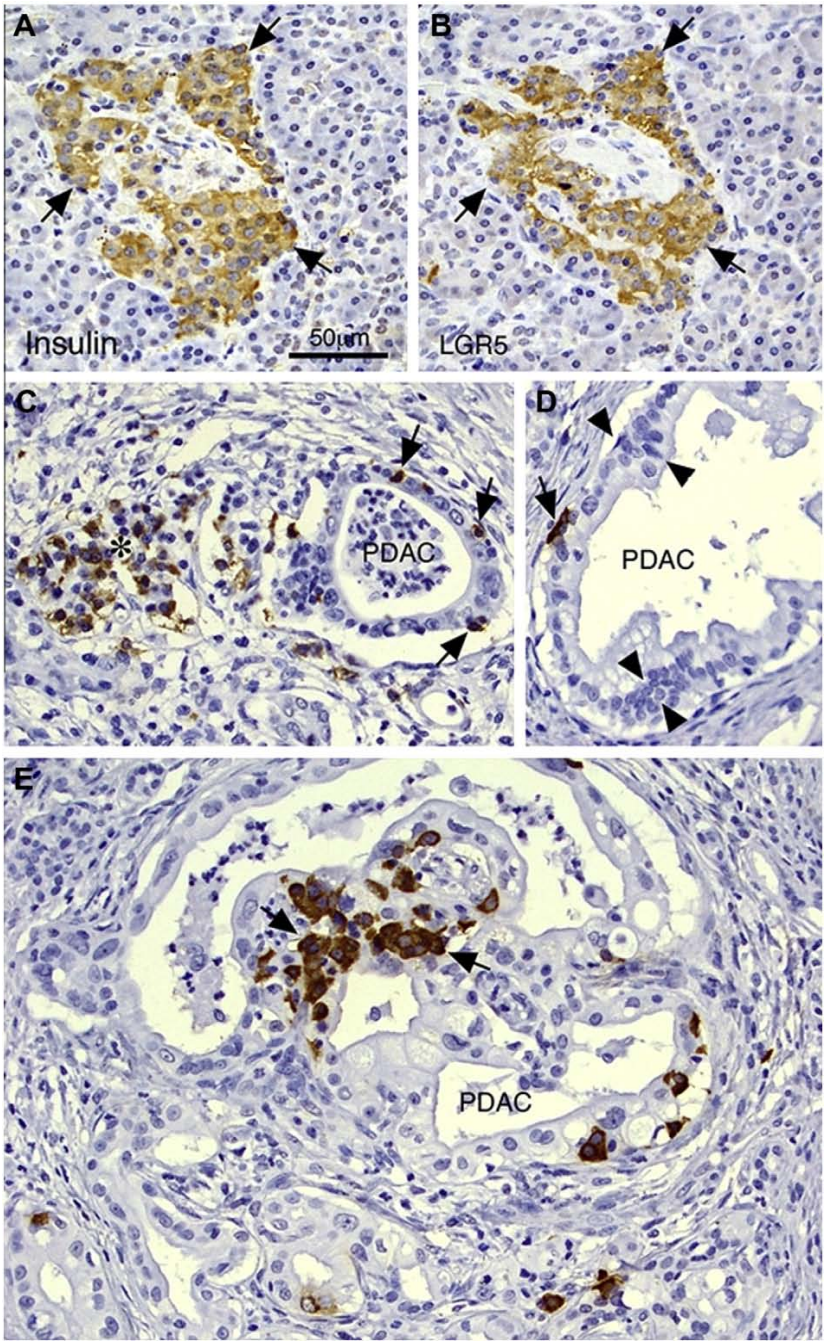

Figure 1. Association of insulin-containing cells with the formation of PDAC. (A–E) Gradual initial disintegration of islet of Langerhans in a pancreatic cancer, still embedded in the exocrine tissue. (A) - Staining with antibodies to insulin (arrows) (B) - Staining with antibodies to LGR5. Note the overlapping pattern of insulin and LGR5 staining (arrows). Serial sections. Original magnifications - x200. (C) - Partially decomposed islet of Langerhans associated with PDAC (asterisks). Note very few insulin-containing cells are integrated in the duct wall (arrows). (D) - Part of a duct containing couple of insulin-containing cells (arrows). The duct wall contains multilayered cells (opposing double arrowhead). (E) - PDAC associated with insulin-containing cells (arrows). Original magnification - x200 (Reprinted from Biochem. Biophys. Res. Commun, 433, Amsterdam, A., Raanan, C., Schreiber, L., Polin, N. and Givol, D, LGR5 and NANOG identify stem cell signature of pancreas beta cells which initiate pancreatic cancer, 157-162., Copyright (2013), with permission from Elsevier).

were used to strictly define cancer stem cells in human colorectal cancer [8]. One of the most striking findings in our paper on the pancreas that the stem cells of the pancreas are the ones which destroy the pancreatic cells and the exocrine cells and hence the transition between different kinds of tissues, which was described recently by Zhang and Weinberg [9], is a novel issue and we are grateful for this very important paper as well as other similar papers [10].

Cancer is one of the most frequent causes of death in human beings when chemotherapy, immunotherapy, surgery and radiotherapy could not prolong the life of the patient, with no rational explanation for the different timetables of the disease progression in individual cases. It seems that in the last phase of the disease symptoms are further accelerated. Between 2011-2015 it was revealed that the co-expression of NANOG, a pluripotent transcription factor of the embryonic stem cell, and LGR5 exists in the cancerous tissue (carcinoma), and the number of the stem cell were increased. This phenomenon was clearly observed first in ovarian cancer and PDAC [2-5] and it was later discovered in the colorectal cancer. The difficulty is to point out the exact time of the onset of the NANOG-LGR5 stimulation of expression, in that the precise timing can be detected only by the gene product, which is poorly immunogenic, and by the peroxidase-immuno-indirect labeling which gives the most accurate signal. At the moment, there is no better way to verify this aspect [11].

Figure 1 shows the association of insulin-containing cells with the formation of PDAC.

DISCUSSION

Until 2014, while seeking for the origin of the pancreatic adenocarcinoma, one of the most lethal cancers, it was strongly and firmly believed among the scientific community that in the adult pancreas, the type of the exocrine and the endocrine tissue are fixed with no possibility for transition between them; therefore the cells that give rise to this cancer must invade from the external milieu of the gland. Our research group decided to follow the most abundant markers of LGR5 and NANOG, located in the β-cells of the endocrine tissue, and to follow its possible migration and fusion with the exocrine cells, which were connected to carcinoma cells already during the first generation of the hybrid cells. This finding, using a simple light microscope and pure antibodies to LGR5 and NANOG in paraffin sections of the appropriate tissue, is the most simple and convenient method to perform such an important experiment. This observation already opens very intriguing problems, some of which were already resolved: 1. Can an adult mature cell change its characteristics upon transformation? 2. Can such a phenomenon support early detection of cancers hard to identify in early stage of development? 3. Can it support an early detection of the disease and then try to cure it?

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CONCLUSIONS

This study on the exciting combination of phosphorylated NANOG and LGR5, which accelerate dramatically cell death of cancer cells, can answer the question whether a fixed combination of oncogenes and other factors of the cancerous tissue has the code for building of cancerous or malignant tissue. On the other hand there may be interaction within the cancerous tissue which completely operates upon diverse mechanism.

Future experiments in this line may open other possibilities for malignant cancer tests in a novel detection. Therefore, the treatment of cancer should be operated individually in each patient because we may yet have to reveal any specific combination between various genes.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest concerning this review.

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