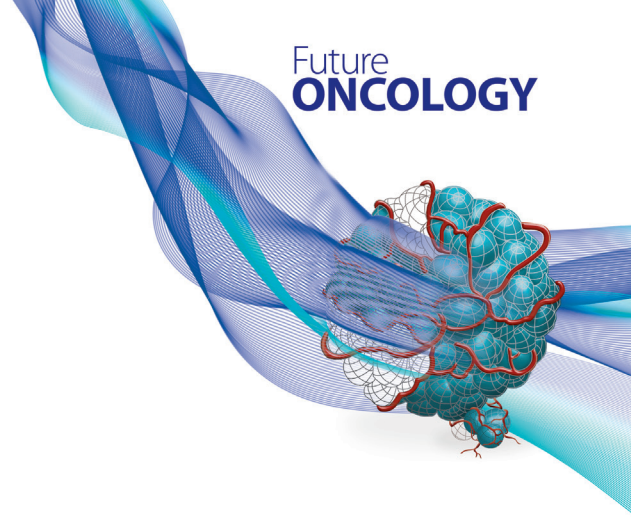
Future ONCOLOGY



EDITORIAL

For reprint orders, please contact: reprints@futuremedicine.com

Fractals: a possible new path to diagnose and cure cancer?

Igor Sokolov*

"...the emergence of fractal geometry in the progression toward cancer was shown only for human cervical epithelial cells. Other cancers have also to be studied to learn how universal the observed fractal behavior could be"

KEYWORDS
• cancer pathways • cervical cancer • fractal • nature of cancer • progression to cancer

The war on cancer is rather far from being victorious. The number of oncology patients has been increasing. In part, it can probably be explained by general aging of human population. There is multiple evidence of correlation between cancer development and polluted environment, genetic predisposition to cancer and exposure to some hazardous chemicals. Nevertheless, the general nature of cancer is not known as of yet. Traditional biochemical studies of cancer seem to be running out of steam. With the increase of precision and speed of DNA sequencing, it has become clear that just standard evolutionary genetic model of cancer may be not enough to understand the nature of cancer [1]. A recently observed sharp increase in the complexity and variability of genetic signatures of activated/mutated genes associated with cancer has considerably slowed the advancement in this direction. There is a hope that physical sciences can provide a missing link to understand and eventually eradicate cancer.

Fractal geometry is one of the intriguing mathematical constructs. If a surface is fractal, its geometry repeats itself periodically at different scales [2]. In 1997, Sedivy and Mader proposed a connection between cancer and fractal [3]. It was justified by the observation that cancer tissues look rather random, chaotic. Fractal, on the other hand, typically occurs when the geometry is formed from chaos (or far-from equilibrium processes, which are quite similar to chaos as well). Indeed, cancer-specific fractal geometry of tumors was found at the tissue scale when analyzing tumor perimeters [4,5]. Fractal geometry was also found in the structure of tumor antiangiogenesis [6,7].

The search for appearance of fractals at the single-cell level is of particular interest. For example, it is still unclear if cancer develops from an individual cell. In the other words, if there is a clear cancer marker for individual cells rather than the entire tumor. A strong correlation between cancer and fractal at the cellular level could be such a biophysical marker. Nevertheless, high-resolution (electron) images of cells did not show the expected transition to fractal geometry when cells become cancerous. Cells derived from cancer and normal tissues demonstrated almost ideal fractal geometry (although having different

"There is multiple evidence of correlation between cancer development and polluted environment, genetic predisposition to cancer and exposure to some hazardous chemicals. Nevertheless, the general nature of cancer is not known as of yet."

*Department of Mechanical Engineering, Tufts University, Medford, MA 02155, USA
and
Department of Biomedical Engineering, Tufts University, Medford, MA 02155, USA
and
Department of Physics, Tufts University, Medford, MA 02155, USA; Igor.Sokolov@tufts.edu

Future Medicine part of fsg

fractal dimension, in other words, the degree of 'roughness' of the fractal surface) [8,9]. Imaging of cells by means of atomic force microscopy (AFM) [10,11] demonstrated higher than SEM resolution of cell surface. It also showed a clear segregation between cancer, immortal (precancerous), and normal cells when using the fractal dimension parameter. However, the use of fractal dimension does not imply presence of fractal geometry. Technically, fractal dimension can be calculated for any surface which is not necessarily fractal.

It is here worth mentioning one important feature of the definition of fractal. Rigorously speaking, fractals are defined for the infinite range of scales, from infinitely small to infinitely large. In reality, it is obviously impossible to obtain an image with infinite resolution and unlimited in size. For example, when imaging cells, the geometric scale is limited by the cell size (~10 µm) and the resolution of the used imaging technique (1–20 nm in the case of the AFM imaging). Therefore, it is plausible to limit the fractal definition to these scales when studying individual cells. This has been done when studying cell fractals.

"It has been found that the fractal geometry on the cell surface (and conceivably, chaos) is reached only at a particular stage of progression to cancer, when premalignant (immortal) cells are transformed into cancerous."

The emergence of fractal geometry on cell surface during progression toward cancer has been finally found in [12], in which human cervical epithelial cells were imaged by a high-resolution AFM technique. The maps of adhesion between the AFM probe and cell surface were analyzed, which can be approximately treated as high-resolution topography images (see [12] for detail). The cervical cell model was chosen as a well-developed system to study development of an epithelial cancer. To better understand what was discovered in [12], let us describe a few technical details. A self-correlation function is used to define fractal and calculate the fractal dimension. The definition of fractal implies that the self-correlation function obeys a power-law dependence on the geometric scale. It can easily be seen as a straight line in the log–log scale. The tilt of that straight line is proportional to the fractal dimension. Divergence of the self-correlation function from this behavior means deviation from being fractal. This deviation was studied in [12].

The results reported in [12] were quite unexpected. It has been found that the fractal geometry on the cell surface (and conceivably, chaos) is reached only at a particular stage of progression to cancer, when premalignant (immortal) cells are transformed into cancerous. Before and after that, geometry of the cell surface deviates from fractal. Normal and cancer cells diverged from fractal in different directions. The parameter of deviation from fractal (called 'multifractality'; multifractality is zero for fractal [12]) was positive for normal and immortal cells (approaching zero for immortal cells), and turn to negative for cancer, crossing zero between immortal and cancerous cells. Contrary to the initial expectations, these results vote in favor of considering cancer (at least, at the cellular level) as rather deterministic development, and not a chaotic disbalance of biochemical reactions (note: this can only be concluded for the reactions which shape the cell surface). At the same time, transition from immortal to cancer cells can be considered as a switch associated with a chaotic disbalance. Later development of cancer is associated with further and further deviation from fractal.

The study of fractal geometry of cell surface performed in [12] was purely physical, nonspecific from biochemical point of view. It is interesting to discuss biomolecular nature of the changes observed. As was shown, the pericellular brush changed substantially when normal cells turn into cancerous [13,14]. The term '(peri)cellular brush' was introduced in [15,16] as the pericellular layer detected by AFM. It consists of glycocalyx (or pericellular coat), microvilli, membrane 'wrinkles' (microridges). When preparing cells for AFM imaging, the cells were freeze-dried. When exposed to ambient humidity, the pericellular brush was collapsed. Thus, the observed surface geometry is topography created by microvilli, microridges and glycocalyx.

It is also interesting to note on geometrical size of surface features which contributes the most to the change of fractal during progression to cancer. Comparing the difference in self-correlation function, which was measured to study fractal as described above, one can see in [12] that the largest changes can be observed at the scale of surface features ranging between 1 and 300 nm. This is quite large scale to speak about difference in particular molecules. It should be clusters of molecules and microvilli's/microridges. Thus, the change in fractal geometry on the cell surface during progression to cancer is presumably associated with aggregates or clusters of microvilli/microridges and glycocalyx molecules. It will be a question of future research to find the reason for such aggregation, to answer if it is caused by changing the chemistry of glycocalyx molecules

or physical property of membrane corrugations (microvilli/microridges), or both.

How these results may be useful? Besides straightforward utilization of the parameter describing deviation from fractal as a new physical biomarker, these results can give some insight for modeling cancer. Next, these results can give some insight for modeling cancer. A nonchaotic behavior of cancer cells votes in favor of models which consider cancer as a switch to another cell behavior rather than chaotic disbalance [17], for example, a switch to an evolutionary regression to the single cell organisms. These results may also bring a new strategy to attack on cancer. For example, it is known that chaotic behavior is typically associated with the existence of points of instability [18], the points which influence chaotic development the most. By disturbing these instability points, it is possible in principle to prevent development of the chaotic behavior. This may open a new avenue to fight cancer. Scientists can start identifying those instabilities in the pathways related to the formation of cell surface. Targeting those points with specific chemicals might prevent the development of the chaotic behavior, and conceivably, to turn the switch to cancer off.

There are obviously many interesting questions remaining to investigate. For example, what exactly the mechanism of the switch, how cancer-promoting chemicals or anticancer drugs influence this switch; if such chemical treatment is an accumulative (deviating immortal cells from cancer is more and more after each treatment), among others. Finally, the emergence of fractal geometry in the progression toward cancer was shown only for human cervical epithelial cells. Other cancers have also to be studied to learn how universal the observed fractal behavior could be.

Financial & competing interests disclosure

This work was partially funded the National Science Foundation grant CMMI-1435655. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1 Weinberg RA. Coming full circle-from endless complexity to simplicity and back again. *Cell* 157(1), 267–271 (2014).

2 Mccauley JL. *Chaos, Dynamics, and Fractals: An Algorithmic Approach to Deterministic Chaos.* Cambridge University Press, Cambridge, UK (1993).

3 Sedivy R, Mader RM. Fractals, chaos, and cancer: do they coincide? *Cancer Invest.* 15(6), 601–607 (1997).

4 Losa GA, NonnenmacherTF, WeibelER. *Fractals in Biology and Medicine (Volume IV).* Birkhäuser, Basel, Switzerland, 175 (2005).

5 Mashiah A, Wolach O, Sandbank J, Uziel O, Raanani P, Lahav M. Lymphoma and leukemia cells possess fractal dimensions that correlate with their biological features. *Acta Haematol.* 119(3), 142–150 (2008).

6 Less JR, Skalak TC, Sevick EM, Jain RK. Microvascular architecture in a mammary carcinoma: branching patterns and vessel dimensions. *Cancer Res.* 51(1), 265–273 (1991).

7 Baish JW, Jain RK. Fractals and cancer. *Cancer Res.* 60(14), 3683–3688 (2000).

8 Meerding WJ, Doornewaard H, Van Ballegooijen M *et al.* Cost analysis of PAPNET-assisted vs. conventional Pap smear evaluation in primary screening of cervical smears. *Acta Cytol.* 45(1), 28–35 (2001).

9 Pierard GE, Ezzine-Sebai N, Fazaa B, Nikkels-Tassoudji N, Pierard-Franchimont C. Karyometry of malignant melanoma cells present in skin strippings. *Skin Res. Technol.* 1, 177–179 (1995).

10 Dokukin ME, Guz NV, Gaikwad RM, Woodworth CD, Sokolov I. Cell surface as a fractal: normal and cancerous cervical cells demonstrate different fractal behavior of surface adhesion maps at the nanoscale. *Phys. Rev. Lett.* 107(2), 028101 (2011).

11 Guz NV, Dokukin ME, Woodworth CD, Cardin A, Sokolov I. Towards early detection of cervical cancer: fractal dimension of AFM images of human cervical epithelial cells at different stages of progression to cancer. *Nanomedicine* doi:10.1016/j.nano.2015.04.012 (2015) (Epub ahead of print).

12 Dokukin ME, Guz NV, Woodworth CD, Sokolov I. Emerging of fractal geometry on surface of human cervical epithelial cells during progression towards cancer. *New J. Phys.* 17(3), 033019 (2015).

13 Iyer S, Gaikwad RM, Subba-Rao V, Woodworth CD, Sokolov I. AFM detects differences in the surface brush on normal and cancerous cervical cells. *Nat. Nanotechnol.* 4, 389–393 (2009).

14 Zhang L, Underhill CB, Chen L. Hyaluronan on the surface of tumor cells is correlated with metastatic behavior. *Cancer Res.* 55(2), 428–433 (1995).

15 Guz N, Dokukin M, Kalaparthi V, Sokolov I. If cell mechanics can be described by elastic modulus: study of different models and probes used in indentation experiments. *Biophys. J.* 107(3), 564–575 (2014).

16 Sokolov I, Iyer S, Subba-Rao V, Gaikwad RM, Woodworth CD. Detection of surface brush on biological cells *in vitro* with atomic force microscopy. *Appl. Phys. Lett.* 91, 023901–023903 (2007).

17 Beerenwinkel N, Schwarz RF, Gerstung M, Markowetz F. Cancer evolution: mathematical models and computational inference. *Syst. Biol.* 64(1), e1–e25 (2015).

18 Meakin P. *Fractals, Scaling, and Growth Far From Equilibrium.* Cambridge University Press, Cambridge, UK (1998).