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Cancer as a "mafia" within the body: A proposition of conceptual approach that seems congruent to the complex biology of the disease

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The effectiveness of our dealings with cancer and its clinical, scientific, and educational aspect depends very much on how we perceive, represent and address its complex biology. Most typically, cancer has been perceived as a sort of an alien. This concept, psychologically justified, since its poses cancer as if an extrinsic enemy, leaves however little room for better understanding its complex relationship with the whole body of the afflicted person. This becomes especially true having in mind what we know about cancer nowadays. This complex relationship between cancer and its host is typically either neglected or at least intentionally underrated. It is necessary to have a way of description of cancer, not only in terms of singular mechanisms (improper signaling, apoptosis) or factors (genetic, environmental) or even issues, like stem cell concept, but visualizing cancer as a holistic and dynamic phenomenon - not as an "alien" but rather "one of us". Cancer cannot be neither reduced nor perceived exclusively in terms of any of the above mentioned issues. On the contrary, the truth of cancer seems to be rather like in Oskar Wilde's statement: (in which the truth is) "rarely pure and never simple". Let us make clear our posit: simplistic conceptual representation of cancer may be practical and even optimism-bearing in terms of doctor-patient relation, however on the other hand, in the long run, especially in case of any failure or complication of treatment, not so effective and even counterproductive. We think that oncologists and any other professionals engaged in cancer research and treatment should have in their mental and conceptual armamentarium a more diversified representation of cancer and also a way to grasp better its reality which would result also in more faithful explanation the intricacy of the disease to the patients. Therefore we want to put forward a concept of cancer as a form of "mafia" within a body. We shall try to explain and convince that it better fits to complicated reality of cancer and may be helpful in both everyday research works as well as in any anticancer educational and prophylactic campaigns. In our opinion this concept much better fits not only to the true nature of cancer, but it also represents cancer-related problems more vividly and simply may better speak to imagination. The thinking of cancer as of mafia within a „society of body", as we will try to convince, invoking only some of the recent reports from the literature on cancer, helps also to explain methodological pitfalls in research on cancer.

By the way, here we would like to mention that we are not the first who juxtapose terms of cancer and mafia. In their seminal review of Maf transcription factors (MafTFs), important for the cancer cells-stroma interactions, Eychene *et al.* facetiously referred to them as "MAFia in cancer" [1]. But in fact there is much more of "mafia" in cancer than just incidental similarity in appellation of the awe-inspiring crime-syndicate and MafTFs. To start our considerations let's pay head to the fact that genetically, cancer cells are by no means "aliens", but very much like mafia members – i.e. not aliens but rather "alienated" from their normal counterparts. As a point of departure let us consider and focus on an example of investigations using RNA microarrays. Nowadays they represent one of the most advanced tools being used in investigation on cancer "wrongdoers". However at closer inspection the microarray of a particular tumor sample is in a sense, rather a sort of a snapshot of a tumor, like that of "mafia et large" made by police detectives. Here we'll allow ourselves to invoke "mafia wedding party" in famous "Prizzi's Honor" with Jack Nicholson and Kathleen Turner. Metaphorically, the process of microarray analysis is very much just like studying a snapshot from such "wedding party". In such a picture surely not all people, as not all cells in a tumor, are notorious malefactors, and not everybody deserves to be incarcerated only by virtue of attending the shady wedding in shady family! One should not forget that mRNAs detected in such microarray belong to both neoplastic cells and admixture of many other cells. Investigators (at least some of them) are aware of this. In an example of prostate cancer, gene expression profiles based on samples obtained by crude dissection may be contaminated by neighboring normal prostate cells, prostate stromal cells, and infiltrating lymphocytes [2]. However, it by no means implies that "non-neoplastic mRNA" in the analyzed samples is meaningless [3]. Other cells in tumor contribute decidedly to its development. Normal cells adjacent to the tumor site secret most of the enzymes involved in extra-cellular matrix (ECM) breakdown. They are involved in neoplastic transformation of cells and tumor clonal expansion by producing growth factors and pro-inflamatory cytokines [4]. Some cells like so called "carcinoma-associated fibroblasts" [5], or "tumor-associated macrophages" [6], or "plasmacytoid dendritic cells" [7] cooperate in a different capacity with "mafia-cancer-criminal-cells" though not doing true "wet work". In particular, so called plasmacytoid dendritic cells behave very much like corrupted policemen, rather protecting, than eliminating "cancer-mafia" [7]. Another tumor-related cells called carcinoma associated fibroblasts (CAFs) microdissected from regions adjacent to human carcinoma show gene expression profile distinct to those in their control group [8]. CAFs may show tumor-promoting phenotype [5,9] through paracrine signaling of CXCR4 and TGF. Similarly, so called glioblastoma-associated stromal

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cells (GASC) have tumor-promoting effects (on cell line A172) [10]. Tumor-associated macrophages (TAMs) produce angiogenic factors, metalloproteases and cathepsins. TAMs have a "trophic" immunomodulatory M2-like phenotype similar to those involved in developmental processes and consistent with the "smoldering nature" of cancer-related inflammation [6,11,12]. Tumor-infiltrating plasmacytoid dendritic cells (pDCs) have immunosuppressive effect in tumor environment inducing IL-10-mediated immunosuppression [7]. Also it is worth to consider that without native macrophages of the brain (microglia) the growth of glioma cells seems to be hampered [13]. Ergo, it turns out that cells like macrophages so far being perceived more as "defenders" against the tumor, act rather like "helpers" or (having in mind "mafia-cancer" analogy) very much like "corrupted policemen".

Taken all together we are deeply aware that many non-neoplastic cells of the host collaborate in "the crime of cancer". But still it is only a part of the truth. So far, the best solution to by-pass an issue of admixture of non-cancerous cells in the sample of tumor is the separation of "criminals" (neoplastic cells) from "innocent" bystanders or those acting "in collusion" by application of laser capture microdissection [2,3]. However, we know that not all true cancer cells are equally dangerous and felonious. Some of them seem only to contribute to a tumor mass, whereas the others can actively invade, destroy and metastasize. Cancer stem cells, supposedly the worst ones, ensure unlimited supply of cancer progeny. The heterogeneity between separate tumor foci results in differences of the grade within the same tumor [2,14], in spite of the fact that, for example in case of prostate, even multifocal cancer has monoclonal origin [15]. What's more, cancer cells when disseminated may change their properties, including the ones so decisive for the efficacy of treatment, like expression of HER2, which may be positive in disseminated breast cancer cells while in the primary tumor the cells were HER2 negative [16]. Definitely these "criminal-cells" behaving in chameleon-like manner make the task of eradication of "cancer-mafia" so difficult and frequently daunting. Many other analogies could be put forward but even only these mentioned above are illustrative for the complexity of cancer biology. Investigating and knowing the single one cancer cell, even in details with its particular signaling pathways putatively involved in acquisition of cancer phenotype does not mean true understanding of disease. Coming back to already discussed laser capture microdissection, one may say that this technique, that can single out a *bona fide* neoplastic cell arguably overcoming the issue of mixed cellular content in the sample, acts in fact like the police arresting the first mafia-member at hand, not at all being sure that they succeeded in apprehension of the most dangerous one. Something cleverer than hasty pinching should be applied, because evidently tumor cells smartly collaborate with the body of the host and like criminals prevaricate when investigated.

As a result, in our opinion, considering all these facts, mafia-cancer concept may be fruitful metaphorical tool that can be used in an explanation of the complicated truth of cancer. It may be useful tool in hands of therapist to convince patient that cancer – like mafia, is not an alien, but in many ways united with body and possessing innumerable relations with non-cancer cells. Therefore not only cancer (i.e., say, tumor) is (should be) the subject of treatment but figuratively the whole body (and mind) should be engaged in a process of struggle and recovery.

Lastly, who knows, maybe all of us who in this or that way and in whatever capacity, try to investigate cancer and/or to treat the patients afflicted with this disease, could take some advantage from real policing strategies applied in fight with the organized crime, of course provided that the policemen are willing to share their methods (know-how) with scientists?

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