

Is Neuroblastoma A Case of Viral Mimicry Suppression?

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Abstract: Generalization and paradigms in Cancer Research are useful but easily lead to conundrums, confusion or paradoxes, as shown here by contraposing two generally accepted “keywords” such as “Targeted Gene Therapy” (TGT) and “Viral Mimicry” (VM). The initial approach to oncogene abnormalities was epitomized by the 1989 Weinberg’s paper: “*throwing monkey wrenches into the clock*”: although we now throw smart small and efficacious molecules, the general approach has not changed. It was believed that curing the gene would cure the disease and nobody asked why such mutations appeared in the first place. We realize today that TGTs are short-lasting. Recently, several groups, working on adult cancers, emphasized the new concept of Viral Mimicry (VM), which sheds new light on the origin of oncogene mutations. Accordingly, oncogene mutations appear as strong suppressors of VM programs: inactivating mutated oncogenes permits the full-blown apoptotic VM program to take place. Initial VM activation is believed to be predominantly associated with dsRNA of Endogenous Elements (EE), but other types of daRNAs have been described. In Neuroblastoma -where VM has been practically ignored- we discovered and isolated a dsRNA virus (MFV) associated with VM death and activation of dsRNA helicases, which is counteracted by DNA amplification of the MYCN proto-oncogene. It is therefore suggested that further research on VM should be extended also to pediatric cancers and especially Neuroblastoma, since it provides a logic explanation for the Darwinian forces, which select for and determine the otherwise unexplainable MYCN amplifications phenomena.

Keywords: neuroblastoma; viral mimicry; MYCN amplification; dsRNA trigger; oncogene aberrations

1. Introduction

In cancer research, we often rely on paradigms or keywords which seem to embody general concepts recognized by most of us as heuristic and generally valid. Paradigms often allow to categorize, to generalize and to associate phenomena which otherwise would appear too chaotic or uncoordinated. Several examples could be made for such an attitude of labeling or set-creating: from “*oncogene-addiction*” to “*targeted-gene-therapy*”, from “*cold or hot-tumors*”, to “*hallmarks of cancer*” to “*actionable cancer mutations*”, and many more.

Although exploiting such generalizations could be helpful, since they immediately provide a conceptual summary, they easily lead to logical contradictions or errors. Most errors derive from: 1. Either the vagueness, imprecision and uncertainty of these definitions or 2. Our uncritical attachment to such keywords, making them fixed-paradigms instead of just hypotheses which should facilitate scientific discussion, but also criticisms, corrections and even falsification. Several examples were made in the past for the “*hallmarks of cancer*” [1–3]: I will focus here on “Targeted Gene Therapy” (TGT) and “Viral Mimicry” (VM).

Started with the figurative imagery of “*tossing monkey wrenches into the clock*” [4], TGTs have evolved for over 25 years in order to achieve greater precision, specificity and potency. As previously discussed, TGT’s major



crux has been *Tumor Heterogeneity* (both inter- and intra-), emphasized already a decade after that start by L. Garraway and C. Swanton groups [5,6].

Therefore, even if we can be much more precise, specific and powerful today in effectively hitting cancer genes, we have learned that such genes often become mobile targets, especially in aggressive cancer cells, in the sense that they mutate or can be bypassed by alternative pathways. Retrospectively however, the initial skepticism (*tossing monkey wrenches*) remains, because the original “causes” of oncogene mutations in cancer cells were not and are still not addressed today, while most of the focus has been on “actionable” cancer genes [7].

Cancer genes appear to respond to very strong Darwinian forces, as it became evident in the last decades [1,3,8–13]. In aggressive cancer, genes seem to behave as “blown-up fuses”: even by changing or repairing one fuse, the next one will soon blow-up. Instead of an endless fuse-repairing/changing, understanding the reason(s) for such continuous blowing-up or *short-circuits* (clearly due to Darwinian forces) would be more appropriate.

2. Oncogene Specific Alterations

‘Why cancer-associated genes and especially oncogenes and TSGs are frequently mutated’ in cancer cells is an often ignored question that we tried to answer throughout the years [3,9,14,15]. Recently, a few groups have associated K-RAS and other oncogene mutations to “*Viral-Mimicry*” (VM) suppression [16]. VM is defined as the induction of an infection-like process which appears to be “endogenous” and therefore typically referred to endogenous retroviral sequences (ERV), transposable elements (TE) or Endogenous Elements (EE) in general, which are harbored inside the genomes of all species of prokaryotes, eukaryotes, vertebrates and mammals, from avian to man [17,18].

However, the origin and evolutionary reasons of VM are not completely clear: Zhou et al. have documented that VM (together with dsRNA accumulation) appears to be suppressed by K-RAS mutations in a model for colorectal cancer (CRC) [16]. The effect of K-RAS mutations is pleiotropic, as also the immune system becomes repressed (for T-cell infiltration, Immune Checkpoint Inhibitors–ICI– therapies, etc.), therefore creating tumors which are “cold” instead of “hot” (*Micro Satellite–MS– Stable*, instead of *Micro Satellite Instability–MSI–High*) and also inhibiting the Interferon–IFN. Pathway (*Interferon Stimulated Genes* or ISGs).

Similar results were also obtained very recently for pancreatic ductal adenocarcinoma (PDAC) and for immunogenic cell death by the groups of D. Altieri and R. de Pinho respectively [19–21]. A legitimate question is therefore whether such cancer-gene mutations (often defined as “*oncogene-addictions*”) may not be the last Darwinian resource that cells utilize in order to escape unavoidable death caused by VM responses [3,22,23].

3. Peculiarities of Neuroblastoma

Neuroblastoma is a rare childhood cancer, which is however important for several reasons: 1. It is the most common extra-cranial tumor in preschool age; 2. Despite its rarity, it causes 15% of mortality among pediatric cancers; 3. Its aggressive forms present in approximately 50% of cases (HR-NB) is still and often incurable; 4. Throughout the past 45 years HR-NB has been at forefront of our basic research and understanding of the molecular mechanisms of cancer, leading to the birth of “precision/personalized” oncology with an avalanche of consequences for most of the other oncology areas [3,9]. Despite advances, several questions still surround this enigmatic pediatric cancer and the molecular aberrations discovered in HR-NB: 1. The high frequency and sometimes evolution of the proto-oncogene MYCN amplification (MNA) [24,25]; 2. The Darwinian forces which cause MNA aberrations (sometimes dramatic) [3,10,13]; 3. The high regression rate of the peculiar form of NB-4S, present in infants diagnosed with neuroblastoma but not at older ages [3,26].

1. MNA is typically described in 20–25% of cases at diagnosis: the extent of amplification appears to be variable, reaching dozens, hundreds or in some cases even over 1000 fold amplifications. The consequences of such amplifications are recognized as dramatically enhanced expression of the transcription factor MYCN. MYCN governs the expression of thousands of genes, typically using the consensus binding-sequence CACGTG (E-BOX) [27,28]. In addition to such amplifications, approximately 10% of NB alternatively amplify enhancer sequences downstream of the c-MYC proto-oncogene, with similar effects of augmented c-MYC transcription factor [29]. In summary, approximately one third of all NB cases amplify this type of oncogenes (MYC), although the Darwinian reasons for this phenomenon are still elusive (see next point) and this phenomenon appears to be widespread, since oncogene amplifications have been confirmed by Turner in approximately 50% of all human cancers [3,30].
2. MYCN gene amplifications are sometimes very large, reaching also 1000 or 1500 copies of amplified DNA. Such dramatic events correspond to derangements of approximately one third of the entire genome, since one amplicon shows a size of approximately 1 Megabase: 10^6 base pairs $\times$ 1000 = the total size is approximately

1 Gigabase. The most accepted molecular models for cancer today are still based on the classical *Hallmarks of cancer* and similar such as the *Bad Luck of Cancer*, which cannot explain such dramatic amplifications and especially the strong Darwinian forces which they imply [3,9,12,13]. Such phenomena are also accompanied by *tumor heterogeneity* both topographic and chronologic, in the sense that MNA may be present only in certain areas of the tumor or MNA may reappear in different subclones and with different extent at subsequent times, even after years [25,31]. A question that the Neuroblastoma field has ignored for too long is: What are the Darwinian forces which determine such dramatic amplifications? Escaping from certain death due to *Viral Mimicry (VM)* is now a logically appealing possibility as I will further discuss [3,22,23].

3. Another unique property of Neuroblastoma is the frequency of regression of tumors which are diagnosed in infancy, the so called Neuroblastoma 4S (also called Stage MS). Although age-thresholds often risk to be imprecise, NB diagnosed infants younger than 18 months display a higher propensity toward spontaneous regression (SR). It is considered the human neoplasia with highest frequency of SR and is generally just monitored by clinicians, which may not even treat the young patients with chemotherapy or other therapies [26,32].

Spontaneous regression (SR) in cancer is typically rare and thus Neuroblastoma, showing the highest frequency of SR, could provide a window of opportunity for understanding its underlying mechanisms. Two major paradigms were generally obtained from SR studies in cancer [33,34]: 1. The immune system appears to be involved, as it has been documented in numerous studies in breast, lung, colon, leukemia and specifically in Neuroblastoma [33,35]; 2. An infection (either viral or microbial) has been typically associated with SR events, especially in historically important settings such as the Cooley's toxin (effective against sarcomas, melanomas, lymphomas and myelomas) and the Bacillus Calmette-Guerrin studied by Lloyd Old –also at MSKCC, NY- and successfully employed till the 70's in the therapy of superficial bladder tumors [33]. The underlying bio-molecular basis for NB-4S are still largely enigmatic, although it is quite clear that only the very young immune system becomes suddenly capable of “rewinding the Ariane's thread” and finding an escape from cancer [26]. Immunologically, the awaking of cellular immunity and especially of NK cells have been invoked in NB-4S and we have proposed an animal model for pre-/perinatal viral infection [3,8,9,36]. Furthermore, extensive mass-screening (MS) studies were performed in the 80's for identifying aggressive forms of HR-NB and thus reducing their associated mortality. However, the unexpected results documented a much higher incidence of NB cases in the MS population (from a frequency of 1:8000 to a frequency of 1: 2000) [37]. The great majority of cases were very low risk and mortality results were unaffected in the MS population [37]. For these reasons MS studies were eventually abandoned [38]. Still these studies suggest that NB cases occur sub-clinically rather often but they then regress spontaneously (SR) [35]. Although 4 types of hypothesis have been previously discussed ([39]), the two previously presented mechanisms with involvement of the immune system and of a previous infection appear to be the most likely for NB4S and for SR in cancer in general [33]. The peculiar chronology of NB 4S -sub-clinical and/or spontaneously regressing in a majority of cases (if occurring at very early age [26])- is consistent with an infectious event such as the one described in the MFV model [3]. In animal models of MFV infection (Fischer 344, Sprague-Dowley etc.), adults are naturally resistant to infection, probably because previously exposed to the virus, while in younger animals the only way to contain MFV spreading is through MYCN oncogene amplification [8,14]. MYCN amplified neuroblasts are resistant to MFV infection, but become highly malignant [9,14]. In neuroblastoma 4S, it is hypothesized that an initial infection leads to containment by immune recognition of viral elements, which occurs later in ontogeny (12–18 months of age). However, when such appropriate immune response is not provided, the only way of the body in order to contain or slow down MFV infection is through MYCN amplification, which also causes viral-mimicry (VM) suppression. Interestingly, prenatal neuroblastoma detected by maternal ultrasounds, also show a behavior similar to NB-4S detected by MS with low risk disease and very good prognosis [40].

4. How Does Neuroblastoma Fit into Viral Mimicry?

- I. How can we make all these observations, some of them obtained long ago and some very recently, fit together?
- II. In neuroblastoma experimental models, we have demonstrated that MYCN amplification is induced by the previous infection with the Micro-Foci inducing virus (MFV), a dsRNA genome Virus belonging to the family of Reoviridae. In in vitro cultures, MFV infected neuroblasts are extensively and rapidly killed (wiped-out) and only neuroblasts which extensively amplify MYCN (up to 100 folds) are capable to survive. The logical consequences of these experiments confirmed for decades [3,8,9,14,15] is at least twofold: A. MFV infection and initial extensive killing provides a very strong selective Darwinian force for the appearance of MNA. This force is similar to the phenomena discovered in pioneering experiments by R. Schimke, F. Alt et al. of selection with metothrexate for the appearance of DHFR gene amplification [41,42]. B. Therefore, in

the HR-NB situation another proto-oncogene aberration (MNA) appears to have a similar role –as oncogenic K-RAS in CRC- for eluding and escaping death by *Viral Mimicry*. In this case, however, the situation seems to be less of a “*mimicry*” and more real: i.e., MFV is a real virus infection which consistently kills cultured cells (and neonatal rats in the Fischer 344 experiments [3,8]).

- III. Viral Mimicry and its elusions and escapes have been studied especially and almost exclusively as promising strategies for helping in cancer therapy [43–45]. The three most accepted and investigated pathways have been: A. the cellular sensors which determine, register and transmit the initial signals which convey the *VM* message to the nucleus B. the chromatin states determined by several effectors (demethylases, acetylases, chromatin remodelers, Polycomb repressors etc. [46–50] which allow expression of previously repressed genes or even non-coding sequences (i.e., dark matter etc. [43]) and C. the initial triggers for eliciting the attention of such sensors and finally the whole process of VM: there is indeed consensus that these are or also contain dsRNA molecules [43,51,52]. We will briefly focus here on the sensors the most accepted pathways for VM induction [53–55]. 1. Many evidence suggest today that *VM* is also determined by sensors of the DEAD/DEAH box family, all characterized by being ATP dependent RNA remodelers (ATPases) and RNA helicases including DDX1, DDX3, DDX21 and DDX42, which also consistently show important roles for antiviral defence, immune regulation and stress response [43,53,56,57]. Interestingly but unexplicably, although some important work was performed in the past in neuroblastoma on DEAD-box helicases [56,57], this subject appears to be “out of fashion” for HR-NB today, just when *Viral Mimicry* becomes a hot subject in other areas. For example, interrogating Pubmed for “Neuroblastoma and Viral Mimicry” for references retrieved none.
- IV. dsRNA is retained by most as the “essential trigger” of VM [23,55,58]. Despite such an agreement, there has been an underlying generalization that dsRNA is mostly constituted by transcribed Endogenous Elements (EE), which are harbored as parasite in all eukaryotes genomes. Although data were also presented for specifically demonstrating the presence of Endogenous Elements (EE) transcription, we still lack a general and consistent demonstration of EE being the essential and exclusive trigger of VM [54,58]. Recently, for example, Altieri et al. as well as Tan et al. demonstrated the presence of dsRNA of mitochondrial sequences [19,59] and in most papers dsRNA is simply detected with J2 antibodies [19] which recognize the dsRNA nature of the Nucleic Acid. Therefore, any type of dsRNA is conceivably present or co-present. In our MFV model (see point 1) we have documented a level of dsRNA specific for MFV, which is at least 1000X higher than in normal mock-infected cells [8]. That this magnified amount of dsRNA is somehow triggering *VM* with extensive cell death in cultured neuroblasts is logically conceivable and probable [3,8].

5. Discussion and Conclusions

The hypothesis presented in this review is based on 1. Previous data obtained by several groups suggesting that viral mimicry (VM) is an important endogenous induction which elicits natural immunity and pro-inflammatory factors, leading to tumor rejection or helping additional anti-cancer strategies [43,45,60]. In this shorter review, however, it was emphasized that such VM effects are typically suppressed in cancer cells. The paradigm considered today is that VM is universally linked to endogenous viral sequences (here discussed as TE, IS, ERV or EE sequences) [51,52,60]. Such sequences are scattered throughout vertebrate genomes and their activation by demethylating/acetylating agents or other means would lead to VM effects; [51,52] 2. In Neuroblastoma, however, we have studied for decades a model in which a very strong effect resembling VM is elicited instead by a dsRNA virus, MFV, initially discovered in a cancer-cluster (i.e., space and time association) of pediatric Neuroblastoma. In this case, however, the dsRNA moiety eliciting the VM effect using typical cytoplasmic sensors [43,53] appears to be viral dsRNA (from MFV). Incidentally, the amount of dsRNA associated with MFV infection is much higher than the amounts shown in the canonical VM papers for Endogenous Elements (EE) [3,8,9,14,51,52].

It is generally acknowledged that two papers on DNA demethylation in cancer cell lines published back-to-back in Cell 2015 have put the basis on VM mechanism for cancer rejection. The first by deCarvahlo’s group [51] shows that demethylating agents induce VM mechanisms in CRC- CICs through dsRNA sensors and MDA5/MVAS/IRF7 axis. It is interesting to observe that even in the first general abstract, the authors state that “*This is associated with induction of dsRNA at least in part from endogenous retroviral elements*”. An increase in dsRNA was shown by the authors using confocal microscopy and the J2 antibody, considered a “*gold standard for dsRNA detection*”. A lower increase in immunofluorescence is shown in Figure 4A,B of paper [51]. However, it was already commented in this review on the lack of specificity of J2 antibodies. The second paper by Chiappinelli et al. on VM activation in Ovarian Cancer (OC) [52] shows dubitative/non-exclusive aspects on the

dsRNA nature even in its title: “...via dsRNA including Endogenous Retroviruses”. In Chiapinelli’s paper, the evidence for a direct involvement of ERV sequences is more limited, as an increase is shown in Figure 5A for approximately 2.5-fold after Aza-Cytine addition or 3–4 times in Figure 5B of paper [52]. We should remember that in the MFV model, the documented increase of specific dsRNA sequences (MFV specific) is at least 100X and in the original tumor 1000X folds [3,8,9]. Similarly, additional more recent papers document the presence of dsRNA of mitochondrial origin and/or they also employ the J2 antibodies which are specific for RNA “doublestrandedness” but not for one particular type of sequence [19,21,59,61].

Therefore, the qualified discussion of this mini-review suggests that, although VM mechanisms are strongly linked to antiviral innate immunity, which is clearly elicited by effectors such as MDA-5, RIG-1, LGP2, PKR, TLR3 etc. [53–55], the nature of the eliciting dsRNA signal is still less clear and should be further clarified. In Neuroblastoma, it is proposed -from the extensive *in vitro* and *in vivo* models [3,8,14,15]—that MFV infection can induce and can be associated with two types of responses: 1. Classical immunity (both natural and probably acquired) which is evident/documentated in animal models in younger adults: after MFV infection, they become lethargic for a few days, but do not show overt disease [3,9,15]; 2. In cell-cultured neuroblasts and in younger animals with an underdeveloped immune system (and more specifically in young pups of infected mothers: i.e., infection by vertical transmission) MFV infection becomes rampant [8]. In these situations, the only lifesaver that infected cells can adopt is to suppress a MFV-viral program by amplifying the MYCN oncogene, sometimes extensively, by 100 or even 1000 folds [3,8,14,15]. Obviously this second cell-adopted “lifebelt” is much less effective, is time-limited and dangerous: 1. The strongly amplified oncogene exponentially activates transcription of genes also involved in proliferation and carcinogenesis; 2. This *escamoutage*, however, and the relative VM suppression programs elicited by MYCN amplification could provide an initial Darwinian advantage -limited in time-: a time-window for the organism to further develop and set-up a more appropriate response (natural and acquired immunity). Such mechanism is what it is proposed it occurs in Neuroblastoma 4S (see previous section). The data and model associating MYCN amplification in pediatric Neuroblastoma with the Viral Mimicry phenomenon are summarized in Figure 1.

FIG. 1 VIRAL MIMICRY HYPOTHESIS IN CHILDHOOD NEUROBLASTOMA

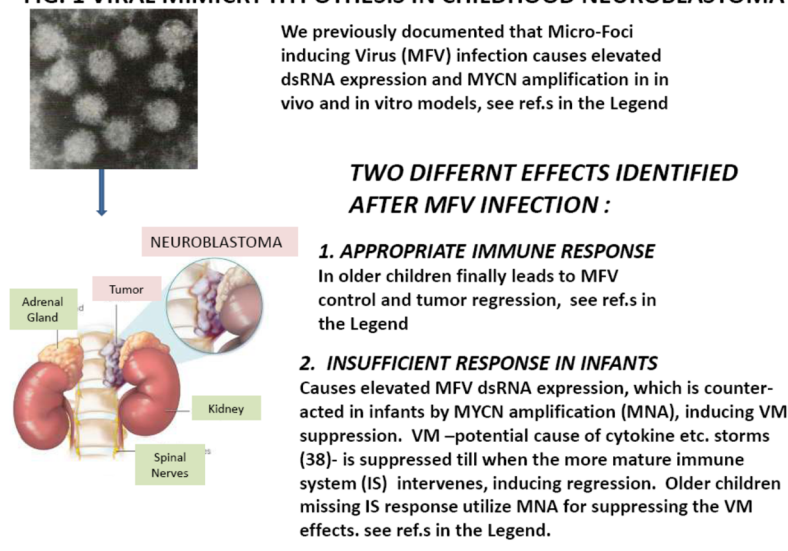


Figure 1. A summary of the concepts presented in this short-review manuscript. The premise is the extensive work (*in vivo* and *in vitro* models for over three decades) characterizing and defining the effects of *Micro-Foci inducing Virus (MFV)* infections, with initial high expression of dsRNA and induction of MYCN amplification (MNA). Our previous work had documented that infection by Micro-Foci inducing Virus (MFV) causes elevated expression of dsRNA and amplifications of the MYCN oncogene in models *in vitro* and *in vivo* [2,8,9,14,15,24]. The association between neuroblastoma and VM suppression by MYCN amplification –basic hypothesis of this shorter review- leads to two different effects: 1. Appropriate Immune Response (IRs) in older children finally leads to MFV control and tumor regression. Refs. [2,8,9,14,15]. Insufficient IRs in infants or older children cause elevated MFV dsRNA expression, which is counter-acted in infants by MYCN amplification (MNA), inducing VM suppression. VM-associated cytokine etc. storms [43] are suppressed till when the more mature immune system (IS) intervenes, inducing regression. Older children missing IS response utilize MNA for suppressing the VM effects. Refs. [20–22,51,52,62]. All these different steps and effects are illustrated by the quoted references.

The association between oncogene aberrations and Viral Mimicry suppression, here epitomized with the example of MYCN amplification in the pediatric tumor neuroblastoma, certainly echoes previous findings obtained with different tumor and oncogene types. In view of the limited space in this mini-review and having started with Dr. F. Marincola two reviewing projects on these subjects, only a few situations will be exemplified.

Beside the already discussed results in Colon-Rectal Cancer (CRC), activating mutations of KRAS in Pancreatic Ductal Adenocarcinoma (PDAC) are present in 94% of cases: an interesting and very clear association of activated KRAS and Viral Mimicry has been demonstrated by Natoli's group. They showed that the KRAS downstream pathway inhibitor Trametinib (it inhibits the downstream KRAS effector MEK1/2), although devoid of effective therapeutic effects (since it eventually elicits genetic resistance) can initially induce Viral Mimicry [62]. Such VM induction is also associated with an initial stimulation of the Interferon (IFN) pathway. Therefore, it remains to be seen whether the new generation of RAS(ON) inhibitors may be capable of inducing a more robust and durable VM effect [63]. Furthermore, the hypothesized VM suppression does not appear to be MYC specific, as it has been described with other oncogene mutations such as the two examples just alluded to [16,62].

Another important (but still not completely answered) question is whether in the MFV model, MYCN amplification (MNA) helps infected cells to survive (for example by inhibiting apoptotic mechanism) or directly suppresses VM. All the preliminary evidence supports the idea that MYCN and MYC oncogenes in general act directly to suppress Viral Mimicry effects. There are some strong evidence: (1) MYCN amplified cells and cell lines MNA+ are shown to be prone to apoptosis induction (not the opposite), so much so that one of the proposed therapeutic strategy is to tilt the precarious equilibrium of MNA+ cells toward overt apoptosis [64]; (2) When Neuroblastoma cells are resistant to apoptosis, it has been shown that the reason is not linked to MYCN or genes of the MYC family (amplification or mutation), but to the silencing of the Caspase-8 gene (either deleted or inhibited by methylation) [65]. Therefore, MYCN function is more likely linked to Viral Mimicry suppression.

Another interesting question is whether MYCN (or MYC family) oncogene amplification is only linked to the proposed Neuroblastoma model (MYCN amplification induced by MFV infection) or it may be also present, possibly in association with Viral Mimicry suppression, in other tumors with MYC family genes amplification. While the MFV model is certainly a prototype of such mechanism(s), mostly because other tumors have not been similarly analyzed or meticulously studied, several potential examples are indeed present. In Hepato-Cellular Carcinoma (HCC), it is recognized that the majority of cases are associated with Hepatitis Virus (generally either B or C) previous infections. High grade disease is associated with amplification of the 8q24 locus containing the cMYC oncogene ([66] and ref.s 6–9 within this paper). Furthermore, there is evidence that such MYC amplified cases are not linked to HCCs triggered by metabolic dysfunction or aflatoxin exposure: they are mostly virally triggered [66]. Furthermore, a few studies have clearly associated HCC with Viral Mimicry phenomena [67] possibly triggered by endogenous retroviruses expression, seen as double-edged sword [68]. Unfortunately, studies similar to the MFV model –carefully following hepatic cells after infection with HBV for appearance of MYC amplification- have not been carried out as yet. However, the most interesting model to be studied-again in this respect is probably Burkitt's lymphoma (BL) with the well-known IgG-MYC translocations (either 8;14 or 2;8 or 8;22) [69]. Although discovered in the 1980's and studied for over 40 years, thus becoming a paradigm for oncogene-associated malignancies [70], several questions are still open [71]. The most relevant here is the role of the virus EBV: although initially discovered during the "lymphoma safari" of Denis Burkitt in Central Africa [72], EBV is not the exclusive or the necessary infectious agent in all cases of BLs. Although present in nearly all African cases of BLs, EBV is absent in the majority of BL cases in Western World (WW) (EBV is absent in 70–90% of WW cases and in 60–75% of HIV-associated BL cases) [73]. Indeed, our still limited studies of cases (in Switzerland) detected BL cases with classical (8;14) and variant (2;14) IgG-MYC translocations, total absence of EBV but presence of viruses related to MFV (MFV-related viruses or MFRVs) [14]. Furthermore, reappraisal of the pioneering work leading to EBV detection (samples were shipped from Africa to London for Electron Microscopy analysis) showed that another type of virus particles were consistently detected by the group of Th. Bell: these particles were indeed of the Reoviridae family (Type 3, similar to MFV) [14,74–76]. Subsequently, this work has been criticized or ignored with assumption that Reoviridae may be often associated with poor hygienic conditions. However, poor hygiene is a very unlikely explanation for our findings in Swiss hospitals at millennium incipit [14]. Still, our current wisdom has to reappraise the extensive lack of EBV sequences/infections in WW cases [73]. In conclusion and as often happens in Science, these important issues deserve more research work in order to clarify the picture.

In conclusion, this mini-review emphasizes the assonance of recent discoveries in VM activation for therapeutic purposes in cancer -where induction of dsRNA sensors leading to innate immunity responses has been clearly documented- with a model for Neuroblastoma with MYCN dramatic amplification. Although discovered long ago and studied for several years [3], this model appears to find new explicatory light in the VM theory [22,23,43]. In

this case however, the emphasis is placed on the VM program repression, since several evidence suggest that oncogene mutations/alterations are indeed associated with processes of “sensors-damping”, chromatin repression, etc. or similar [16,22,23,63]. Furthermore, the nature of the dsRNA trigger is placed into question, since the evidence for the exclusive presence of Endogenous Elements (EE) dsRNAs as triggers is scanty and evidence for additional dsRNA is already documented, including mitochondrial and MFV dsRNA [3,9,19,59].

The picture presented in this short review somehow recaps over thirty years of work ([3,8,9,14,15] and debating on the origin of specific aberration in Neuroblastoma cells (and by inference of additional cancer types). In this longer lapse of time, while everybody asked how to “toss monkey wrenches into the clock...”, we asked instead a very simple and short question: “why...?”. Finally, a potential answer is now emerging thanks to the work of several egregious groups with the concept of *Viral Mimicry (VM)* [22,23,43]. However, our group’s work suggests a “slight-bent” to the original *VM* concept, which has been mostly based on the idea that endogenous elements (EE) expression -widespread through the genome- is typically and exclusively linked to *VM* [58]. Data from our group on Neuroblastoma cases diagnosed in a cancer-cluster indicate instead that a dsRNA virus is a potential trigger [3,8,9]. Whether this model may be applicable to additional cancer types (also adult) is possible. We suggested in the past additional tumors showing cellular and molecular features similar t Neuroblastoma, such as Small Cell Lung Carcinoma (SCLC) and Neuro-Endocrine Prostate Cancer (NEPC) as potential candidates for initially searching for MFV-like mechanisms of adult carcinogenesis [77]. Additional potential association with Western World (WW) Burkitt Lymphoma (BL) have been summarized also in this discussion [14]. Further data and research is therefore warranted, since in this case VM more than an “imitation” (*mimicry*), appears to be a real infection (also vertically transmitted [3,8,9]): there are therefore strong implications for an initial trigger and for Darwinian evolution.

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