DIVERSITY OF RIBONUCLEIC ACID (RNA) VIRUS ENDOGENOUS VIRAL ELEMENTS (EVEs) IN INSECT GENETIC MATERIAL

Muhammad Saqib, Najma Bibi, and Sawaira Bibi.

Department of zoology, University of Education, Lahore, DG Khan Campus, DG Khan, Pakistan

saqibmoosa58@gmail.com

Article received 14.2.2022, Revised 30.5.2022, Accepted 6.6.2022

ABSTRACT
Many different RNA viruses infect insects, but the capacity to transmit to a single or numerous host species sets them apart. Through recipient transcription and replication, viral chromosomes may be incorporated into their host genes, resulting in the emergence of endogenous viral elements (EVEs). It has proven possible to find RNA virus EVEs in various of insect genomes with varying evolutionary paths, from extremely damaged genetic remnants to partial and full viral coding sections, in several different insects. Insect–virus contact has benefited much from research on these EVE, such as developing a novel kind of intuitive antiviral immunity. From a functional standpoint, RNA EVEs' effects on hosts and migratory viruses are still mostly unknown. However, new research shows that they are involved in a complicated arms race that affects the genetic path of these interdependent organisms. As additional insect genotypes and extrinsic viral are decoded, the variety of insect EVEs will continue to grow, making paleoviropale生物学 exciting study area for insects in the coming years.

Keywords—RNA viruses, EVEs, Insect genomes, Evolutionary pathway, Host genome.

INTRODUCTION

A viral genetic material or portion of a viral genetic material that is incorporated into the host chromosome is referred to as an endogenous viral elements (EVE). Transposable elements (Retroviruses) and caulimoviruses (Caulimovirus-ses) were the primary focus of initial EVE research (Navani et al., 2021). Going into the new millennium, findings of EVE generated from additional viral groups appeared, including those in insects (Ahmad et al., 2020, Chen & Xu, 2020), supplemented by larger-scale investigations of EVE inherited from numerous viral families in different eukaryotic genomes (Yang et al., 2017, El housse, Hadfi, Karmal, Ben-aazza, et al., 2021). A miRNA repository has been established, miR-Base (Rabi-zadeh et al., 2019), which contains the sequences of thousands of microRNAs, including several from insects. The identification additional mi-RNAs has led to a greater knowledge of their production (Zuo et al., 2020). Non-canonical miRNA assembly routes have since been identified, for example, in contrast to the canonical process. A number of them include the creation of miRNAs from introns (known as mirtrons), ribonucleic RNAs, transfer RNAs, and endo-siRNAs (Chen et al., 2015). It is recommended miRNA synthesis in insects refer to certain other recent articles (Wang et al., 2017 and El housse, Hadfi, Karmal, EL Ibrahimimi, et al., 2021). Insect-borne wheat viruses presented a severe danger to grain output in several maize nations from the mid-1950s through the 1980s (Jana et al., 2021). Recently, researchers in Shandong have discovered two new wheat viruses: SRBSDV and the RSMV (Rice Stripe Mosaic Virus). Relationships between EVEs and braconid wasps have developed over 74 million years, so much so that the line between the two creatures has been blurred.

Nudiviruses, a virus family that induces persistent infection in insects’ hormonal imbalance, have been hypothesized to be EVEs ancestors (Urban et al., 2018). The discovery of nudivirus-like genes in the collected semi-structured genomes, verified by comprehensive sequence data and computational analysis, solidified the nudiviral origins of EVEs. In either a continuous or nearly continuous way, these wheat infections are transmitted by predatory insects or plant hoppers. The translation of miRNA loci in the nuclei is the first step. A miRNA synthesis site may be obtained from a viral genome transcriptome, nucleotide sequenc-es, or protein-coding sequences (Hannafon, 2021, Treviño-Villarreal et al., 2021). Rice viral infections can only be controlled in the field by fully comprehending the processes that allow viral transmission through insect vectors. As a consequence, the major parts of these micro-RNA-coding subunits are translated by RNA polymerase II and yield primary-miRNA transcripts that include one or more stem-loop configurations (pri-miRNA). When viruses infect
cells, the tran-scription of host protein-coding genetic makeup and microRNAs are altered to facilitate the virus's growth and replication. Viruses have acquired the ability to encapsulate miRNAs, which they exploit to dampen the host antiviral response (Müller et al., 2021, Shibata et al., 1990). Viruses have a distinct advantage in using miRNAs as weapons due to their small size, non-antigenic nature, and ability to influence host and own genomes. However, only infections with DNA sequences have been proven to synthesize miRNAs, which means that not all infections transmit miRNA. Due to the RNA genome's vulnerability to RNase III-type enzymes, the question of whether RNA viruses can encode for miRNAs is currently open (Iozzo et al., 2021). Structure-specific and non-structure-specific nrEVEs may persist and replicate in the host genome, as demonstrated in previous studies (Bernard & Wellberg, 2021). According to current research, exogenous nrEVEs may persist and replicate in the host genome. Viral resistance may be linked to nrEVEs. This can be done, for example, by expressing indigenous Bornavirus-like nucleoproteins, which have been discovered in numerous somatic mutations as well as in the wing-foldding and mortality since (Rubenich et al., 2021). The Israeli acute paralytic viruses (IAPV, dicistrovirus) were discovered to have comparable performance in Apismellifera that had a sequence derived from IAPV (Ibrahim et al., 2015). CRISPR-Cas, regulating the expression of nucleic acids and viral genes that were reprocessed and now play critical roles in host biology, has all emerged as a result of a continuous arms race between viruses and their hosts (Wu et al., 2020, Coffelt et al., 2015). However, until recently, scientists noticed that viral-derived sequences incorporated into the host genome had a significant influence on the mechanics of the space race and the biology of the host (Youn et al., 2012). As a result of this research, it is considered essential to contribute to an understanding of viruses and how host-virus interactions have affected eukaryotic organisms' development, especially via viral endogenization. Our goal is to summarize the variety of EVE that has already been discovered in insect chromosomes so far and compare it to the differences in the structure of exogenous insect viruses to supplement earlier studies on insect EVE (Powell & Huttenlocher, 2016, Puga et al., 2012). As a result of the various methodologies used to describe these two forms of EVE, we have successfully presented them individually: those derived from big dsDNA infections as well as those derived from other viruses.

Does viral infection alter the host's miRNA profile in any way?

First, numerous studies have shown that infection alters the host's miRNA profile, with consequences ranging from subtle to severe, depending entirely on the host and virus combinations. Baculoviruses (Lämmermann et al., 2013, Mishalian et al., 2014), an ascovirus (Kow-anetz et al., 2010), a cytoplasmic polyhedrosis virus (Wislez et al., 2001), West Nile virus (WNV) (Ardi et al., 2007), chikungunya virus (Ma et al., 2013) and dengue virus (DENV) (Casbon et al., 2015) have been demonstrated to have different levels of host miRNA expression. As a result of a viral illness or the virus's modification of the host, transcriptional and genomic amplicon tech-iques have shown alterations in gene expression. The Amsatochromeontomopoxvirus and other poxviruses have shown to be degraded by host miRNAs by polyadenylation using a virus-encoded poly (A) polymerase (van der Windt et al., 2018). Although the polyadenylated host miRNAs are degraded due to this process, siRNAs are protected by 2′O-methylation and so are not affected by this mode of degradation. In addition to the many characteristics of mature snRNAs, these routes have various signatures: There are two distinct types of DNAs-derived RNA: which are single-stranded DNAs and double-stranded DNAs (Quigley & Deryugina, 2012). Subverting the number of host miRNAs, which in certain circumstances act as therapeutic strategies, areoneway viruses evade the immune system. In the same way as Ran, a guanylyl imido-diphosphate, guanosine-5′-triphosphate, or guanosine triphosphate (GTP-binding) nuclear protein, is downregulated by Bombyx mori Nuclear Polyhedrosis (bmpnv-mir-1), the host defense is modulated by a similar method of reducing the miRNA population by inhibiting the expression of the transcription of Ran. The exportin-5-mediated small RNA transport mechanism relies heavily on this enzyme. The degradation of GTP by Ran supplies energy to exportin-5. Despite this, bmpnv-mir-1 was anticipated to have a peptide bond on the 3′ untranslated region (UTR) of Ran mRNA, and luminescence and in vitro research in B. mori larvae confirmed this relationship (Najmeh et al., 2017, Shiara et al., 2011). Alternative snRNA biogenesis has been hypothesized in conjunction with the discoveries of virus- and EVE-generated snRNAs.
snRNAs from endogenous viral sequences: discovery and function

Virus-encoded miRNAs (vmiRNAs) tend to be less abundant than siRNAs during viral infection often triggers death (Shaul & Frid, 2008). Thus, RNA viruses could not produce miRNAs because their replication and replication in carrier cells, Rice gall dwarf virus (RGDV) particles also gathered around deteriorated mitochondria (Jin & Esteva, 2008). Thus, RGDV infection can lead to mortality in insect vector cells by depleting mitochondrial dysfunction. These miRNAs, bmnpv-let-7, were considered as candidates for the host RNomes, including four B. mori miRNAs. Similarly, deox-ribonucleotide Ran depletion resulted in a significant intensification of host miRNAs (Di Maio et al., 2005). However, phagocytosis and death are kept to minimize evident insect disease and sustain continuous viral propagation (Figure 1). These processes work together to maintain a thermodynamically stable equilibrium between viral abundance and virulence, enabling the virus to remain in insects. Insects manage the balance of apoptotic, phagocytosis, c-Jun N-terminal kinases (JNK), and siRNA systems in response to virus infection (Bekes et al., 2011).

**RNA viruses**

Recently, researchers detailed the various viral spread mechanisms (Strell et al., 2010, Singh et al., 2012). This article focuses on non-circulative, semi-persistent (NCSP) transmission regarding NCNP and C-type natriuretic peptide (CNP) transfer (Nathan, 2006). It is possible to acquire NCNP viruses from a fungal pathogen and to transmit them to a recipient species after a brief acquisition bandwidth utilization and an inoculated accessibility period (IAP) (Hazafa et al., 2021). Displacement is lost when the vector molts, and viral circulation (transit) through the carrier is not required for dissemination (Han et al., 2012). Most CNP viruses are phloem-specific, meaning they are obtained from and transmitted to the phloem by lengthy (minutes or hours) AAPs. As a result, they must circulate via their carriers for a lengthy period before being injected into the target species (Shaul & Fridlender, 2019). NCSP viruses have characteristics similar to NCNP and CNP viruses, such as phloem tropism and lengthy AAPs and IAPs. Their retention spans are longer than NCNP viruses' (hours to days), but they lose airborne transmission when the vector molts (Kwiatkowski, 2015). Previously, it was thought that RNA viruses could not produce miRNAs because their
genomes or replicative forms could be eliminated by complementary adosorption of miRNAs and because most RNA viruses replicate in the cytoplasm, which lacks Drosha (Youn et al., 2008, Chung et al., 2013). Endogenous miRNAs can be generated from duplicated pre-miRNAs via RNA virus recombination without harming the virus genome (Rayes et al., 2015), and Drosha may not enter the nucleus if chronic inflammation causes Drosha to enter the cytoplasm. Several articles reported miRNAs encoded by several RNA viruses. A phage (HIV-1; discussed (Stark et al., 2005, Reiman et al., 2007) in produced the very first ribosome virus encoding miRNAs, but these have been questioned (Houghton et al., 2010) owing to low read counts of tiny RNAs identified in deep sequencing. The lack of miRNA commonality between Cotesia and Microplitisbracoviruses shows that these Polyhedra-Derived Virus (PDV) miRNAs were obtained separately or created after Cotesia and Microplitis diverged. It’s worth noting that six PDV emiRNAs (including offerings that are compatible with an abundantly expressed insect miRNA) have miRbase mappings and are evolutionarily similar to miRNAs from the point (Molinedo, 2019). In larvae, inhibiting bmnpv-miR-1 with LNA had a deleterious effect on BmNPV load. While bmo-miR-8, a putative cellular miRNA, was inhibited, the BmNPV load spiked, indicating the antiviral nature of host-miRNAs. The suppression of host antiviral miRNAs by bmnpv-miR-1 was shown to be essential for infection establishment in B. mori (Eruslanov, 2017, Yamanaka et al., 2007). Since Insect-Specific Viruses (ISVs) have mostly been found in all 4 phases of the mosquito life cycle, it appears that vertical transfer from females to their progeny is the most common method of EVEs propagation. There are two ways that EVEs and viral diseases maintain themselves in nature: by transovarial transmission, where the viruses infect vectors’ germ cells processes, and through the transfer of the infections to mosquitoes’ offspring. There is also a transocular process through which the virus infects the eggs as they travel through the oviduct (Nguyen et al., 2021). Neither the nudivirus nor the baculovirus genomes contain homologs. So far, the source of the new CvBV miRNAs is currently unexplained.

**Conclusion and future research directions:** The virus–insect co-evolutionary arms race might now be significantly impacted by the multiple interactions between RNA viruses and insects. NIRV-derived regulation influences host resistance and vector illustration competency. piRNA regulates complementary viral replication, influencing host resistance and vector competency. The influence of non-retroviral integrated RNA virus sequences (NIRVS) on host virus physiology in realistic insect virus environments has to be studied further. Non-retroviral integrated RNA virus sequences (NIRVS) emerging is a regular occurrence, and our present understanding touches the surface of non-retro-viral integrated RNA virus sequences (NIRVS) in insects. Too far, insects’ EVE has viruses from three major dsDNA viral families, at minimum Fourteen of the 23 big RNA virus clades identified and four big ssDNA virus families. This variety is common in arachnids but rare in mammals. Many EVE is genetically linked to an existing endogenous virus, and several may be put in their own distinct family, which otherwise would have led to extinction. Also, new viruses discovered by large-scale genomics and proteomics will be used as bait in homology searches, substantially expanding the insects’ EVE repertoire. The insect EVE environment seems to be very dynamic, and its research will likely add to our knowledge of insect–virus relationships in the coming years. It will be easier to detect multigene EVE originated from Poxviridae and Iridoviridae, which are widely distributed in insects, and to trace the history of big dsDNA viral selective breeding in hymenopteran and non-hymenopteran insects using novel EVE inspection processes. Like in the case of The Aedes aegypti mosquito it will be important to assess the percentage of EVE that affect host fitness and their potential roles. In wild vector mosquitoes, whether EVE-derived antiviral resistance influence the development of viral pathogens and if changes in this route alter vector competency are critical questions. Aside from genomc quantity and genome assembly quality, the EVE environment seems to be significantly different across insect species.

**REFERENCES**

Navani N, O’Dowd E, Succony L, Karahacioglu B, Rintoul R, Woolhouse I, Evison M, Fuller E, Bhamani A, Janes S, Eccles S, Baldwin D: The impact of COVID-19 on lung cancer diagnostics—a multicentre comparison of 2019/2020 data. Lung Cancer, Elsevier B.V. 156:S19–S20 (2021).

Ahmad M, Iram K, Jabeen G: Perception-based influence factors of intention to adopt COVID-19 epidemic prevention in China. Environ Res Elsevier Inc. 190:109995 (2020).

Chen L, Xu X: Effect evaluation of the long-term care insurance (LTCI) system on the health
care of the elderly: A review. J. Multidiscip. Healthc., Dove Medical Press Ltd Pp. 863–875 (2020).

Yang L, Yang W, Xu B, Yin X, Chen Y, Liu Y, Ji Y, Huan Y: Synthesis and scale inhibition performance of a novel environmental friendly and hydrophilic terpolymer inhibitor. Des-alination Elsevier B.V. 416:166–174 (2017).

El houss M, Hadfi A, Karmal I, Ben-aaiza S, Belattar M, Errami M, Mohareb S, Driouiche A: Study of the effect of inorganic inhibitor on the calcium carbonate precipitation in the localized irrigation systems. Nanotechnol Environ Eng, Springer Science and Business Media Deutschland GmbH 6 (2021).

Rabizadeh T, Morgan DJ, Peacock CL, Benning LG: Effectiveness of Green Additives vs Poly(acrylic acid) in Inhibiting Calcium Sulfate Dihydrate Crystallization. Ind Eng Chem Res, American Chemical Society 58:1561–1569 (2019).

Zuo Y, Yang W, Zhang K, Chen Y, Yin X, Liu Y: Experimental and theoretical studies of carbo-xyllic polymers with low molecular weight as inhibitors for calcium carbonate scale. Crystals, MDPI AG 10 (2020).

Chen J, Xu L, Han J, Su M, Wu Q: Synthesis of modified polyaspartic acid and evaluation of its scale inhibition and dispersion capacity. Desalination Elsevier 358:42–48 (2015).

Wang Y, Li A, Yang H: Effects of substitution degree and molecular weight of carboxymethyl starch on its scale inhibition. Desalination Elsevier B.V. 408:60–69 (2017).

El houss M, Hadfi A, Karmal I, EL Ibrahim B, Ben-aaiza S, Errami M, Belattar M, Mohareb S, Driouiche A: Experimental investigation and molecular dynamic simulation of Tannic acid as an eco-friendly inhibitor for calcium carbonate scale. J Mol Liq, Elsevier 340:117225 (2021).

Jana S, Muscarella RA, Jones D: The Multi-faceted Effects of Breast Cancer on Tumor-Draining Lymph Nodes. Am J Pathol, 191:1353–1363 (2021).

Urban F, Siciliano G, Wallbott L, Lederer M, Dang Nguyen A: Green transformations in Vietnam’s energy sector. Asia Pacific Policy Stud, John Wiley and Sons Ltd, 5:558–582 (2018).

Hannafon BN: Involvement of the Tumor Microenvironment in the Pathogenesis of Breast Cancer. Am J Pathol. Elsevier Inc. 91:1328–1329 (2021).

Treviso-Villarreal JH, Reynolds JS, Langston PK, Thompson A, Mitchell JR, Franco RA: Down-Regulation of a Profibrotic Transforming Growth Factor-β1/Cellular Communication Network Factor 2/Matrix Metalloproteinase 9 Axis by Triamcinolone Improves Idiopathic Subglottic Stenosis. Am J Pathol, Elsevier Inc. 191:1412–1430 (2021).

Müller C, Rosmark O, Åhrman E, Brunström H, Wassilew K, Nybom A, Michaliková B, Larsson H, Eriksson LT, Schultz HH, Perch M, Malmström J, Wigén J, Iversen M, Westergren-Thorsson G: Protein Signatures of Remodeled Airways in Transplanted Lungs with Bronchiolitis Obliterans Syndrome Obtained Using Laser-Capture Microdissection. Am J Pathol, Elsevier Inc. 191:1398–1411 (2021).

Shibata D, Almoguera C, Forrester K, Dunitz J, Martin SE, Cosgrove MM, Peruco M, Arnheim N: Detection of c-Kras Mutations in Fine Needle Aspirates from Human Pancreatic Adenocarcinomas. Cancer Res 50:1279–1283 (1990).

Izzo M, Sgrignani G, Comito G, Chiarugi P, Giannoni E: Endocannabinoid System and Tumor Microenvironment: New Intertwined Connections for Anticancer Approaches. Cells [cited 2021 Dec 7], 10:3396 (2021). Available from: https://www.mdpi.com/2073-4409/10/12/3396

Bernard JJ, Wellberg EA: The Tumor Promotional Role of Adipocytes in the Breast Cancer Microenvironment and Macromolecule. Am J Pathol. 191:1342–1352 (2021).

Rubenich DS, Omizzollo N, Szczepański MJ, Rei-cher T, Whiteside TL, Ludwig N, Braganhol E: Small extracellular vesicle-mediated bidi-directional crosstalk between neutrophils and tumor cells. Cytokine Growth Factor Rev, Pergamon 61:16–26 (2021).

Ibrahim SA, Katare GK, Kulshrestha A, Jaiswal MK, Amin MA, Beauman KD: Breast cancer associated α2 isoform vacuolar ATPase immunomodulates neutrophils: Potential role in tumor progression. Oncotarget, Impact Journals LLC 6:33033–33045 (2015).

Wu M, Ma M, Tan Z, Zheng H, Liu X: Neutrophil: A New Player in Metastatic Cancers. Front Immunol, Frontiers Media S.A. 11 (2020).

Coffelt SB, Kersten K, Doornebal CW, Weiden J, Vrijland K, Hau CS, Verstegen NJM, Ciampricotti M, Hawinkels LJAC, Jonkers J, De Visser KE: IL-17-producing γδ T cells
and neutrophils conspire to promote breast cancer metastasis. Nature, Nature Publishing Group, 522:345–348 (2015).

Youn J-I, Collazo M, Shalova IN, Biswas SK, Gabrilovich DI: Characterization of the nature of granulocytic myeloid-derived suppressor cells in tumor-bearing mice. J Leukoc Biol. 2012, 91:167–181 (2012).

Powell DR, Huttenlocher A: Neutrophils in the Tumor Microenvironment. Trends Immunol, Elsevier Ltd 37:41–52 (2016).

Puga I, Cols M, Barra CM, He B, Cassis L, Gentile M, Comerma L, Chorny A, Shan M, Xu W, Magri G, Knowles DM, Tam W, Chiu A, Bussel JB, Serrano S, Lorente JA, Bellosillo B, Lloreta J, Juanpere N, Alameda F, Baró T, De Heredia CD, Torán N, Catalá A, Torredablé M, Fortuny C, Cusí V, Carreras C, Diaz GA, Blander JM, Faber CM, Silvestri G, Cunningham-Rundles C, Calvillo M, Dufour C, Notarangelo LD, Lougaris V, Plebani A, Casanova JL, Canal SC, Diefenbach A, Aróstegui JI, Juan M, Yagüe J, Mahlaoui N, Donadié J, Chen K, Cerutti A: B cell-helper neutrophils stimulate the diversification and production of immunoglobulin in the marginal zone of the spleen. Nat Immunol 13:170–180 (2012).

Lämmermann T, Afonso P V., Angermann BR, Wang JM, Kastenmüller W, Parent CA, Germain RN: Neutrophil swarms require LTB4 and integrins at sites of cell death in vivo. Nature 498:371–375 (2013).

Mishalian I, Bayuh R, Eruslanov E, Michaeli J, Levy L, Zolotarov L, Singhal S, Albelda SM, Granot Z, Friedlinger ZG: Neutrophils recruit regulatory T-cells into tumors via secretion of CCL17 - A new mechanism of impaired anti-tumor immunity. Int J Cancer 135:1178–1186 (2014).

Kowanetz M, Wu X, Lee J, Tan M, Hagenbeek T, Qu X, Yu L, Ross J, Korsisaari N, Cao T, Bou-Reslan H, Kallop D, Weimer R, Ludlam MJC, Kaminker JS, Modrusan Z, Van Bruggen N, Peale F V., Carano R, Meng YG, Ferrara N: Granulocyte-colony stimulating factor promo-tes lung metastasis through mobilization of Ly6G+Ly6C+ granulocytes. Proc Natl Acad Sci USA 107:21248–21255 (2010).

Wislez M, Fleury-Feith J, Rabbe N, Moreau J, Cesari D, Milleron B, Mayaud C, Antoine M, Soler P, Cadranel J: Tumor-derived granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor prolong the survival of neutrophils infiltrating bronchoalveolar subtype pulmo-nary adenocarcinoma. Am J Pathol 159: 1423–1433 (2001).

Ardi VC, Kupriyanova TA, Deryugina EI, Quigley JP: Human neutrophils uniquely release TIMP-free MMP-9 to provide a potent catalytic stimulator of angiogenesis. Proc Natl Acad Sci USA 104:20262–20267 (2007).

Ma Y, Adjemian S, Mattarollo SR, Yamazaki T, Aymeric L, Yang H, Portela Catani JP, Hannani D, Duret H, Steegh K, Martins I, Schlemmer F, Michaud M, Kepp O, Sukkurwala AQ, Menger L, Vacchelli E, Driou N, Galluzzi L, Krzyziesk R, Gordon S, Taylor PR, Van Endert P, Solary E, Smyth MJ, Zitvogel L, Kroemer G: Anticancer chemotherapy-induced intratumoral recruitment and differen-tiation of antigen-presenting cells. Immunity 38:729–741 (2013).

Casbon AJ, Reynau D, Park C, Khu E, Gan DD, Schepers K, Passegué E, Werb Z: Invasive breast cancer reprograms early myeloid differentiatiation in the bone marrow to generate immunosuppressive neutrophils. Proc Natl Acad Sci USA, 112:E566–E575 (2015).

van der Windt DJ, Sud V, Zhang H, Varley PR, Goswami J, Yazdani HO, Tohme S, Loughran P, O’Doherty RM, Minervini MI, Huang H, Simmons RL, Tsung A: Neutrophil extra-cellular traps promote inflammation and de-velopment of hepatocellular carcinoma in non-alcoholic steatohepatitis. Hepatology 68: 1347–1360 (2018).

Quigley JP, Deryugina EI: Combating angiogenesis early: Potential of targeting tumor-recruited neutrophils in cancer therapy. Futur Oncol 8:5–8 (2012).

Najmeh S, Cools-Lartigue J, Rayes RF, Gowing S, Vourtzoumis P, Bourdeau F, Giannias B, Berube J, Rousseau S, Ferri LE, Spicer JD: Neutrophil extracellular traps sequester circulating tumor cells via $\beta 1$-integrin mediated interactions. Int J Cancer140:2321–2330 (2017).

Shitara K, Matsuo K, Oze I, Mizota A, Kondo C, Nomura M, Yokota T, Takahari D, Ura T, Muro K: Meta-analysis of neutropenia or leukopenia as a prognostic factor in patients with malignant disease undergoing chemotherapy. Cancer Chemother Pharmacol 68:301–307 (2011).

Shojaei F, Wu X, Zhong C, Yu L, Liang XH, Yao J, Blanchard D, Bais C, Peale F V., Van Bruggen N, Ho C, Ross J, Tan M, Carano RAD, Meng YG, Ferrara N: Bv8 regulates
myeloid-cell-dependent tumour angiogenesis. Nature 450:825–831 (2007).

Akizuki M, Fukutomi T, Takasugi M, Takahashi S, Sato T, Harao M, Mizumoto T, Yamashita JI: Prognostic significance of immuno-reactive neutrophil elastase in human breast cancer: Long-term follow-up results in 313 patients. Neoplasia 9:260–264 (2007).

Huang QT, Man QQ, Hu J, Yang YL, Zhang YM, Wang W, Zhong M, Yu YH: Prognostic sig-nificance of neutrophil-to-lymphocyte ratio in cervical cancer: A systematic review and meta-analysis of observational studies. Oncotarget 8:16755–16764 (2017).

Wculek SK, Malanchi I: Neutrophils support lung colonization of metastasis-initiating breast cancer cells. Nature 528:413–417 (2015).

Shojaei F, Wu X, Qu X, Kowanetz M, Yu L, Tan M, Meng YG, Ferrara N: G-CSF-initiated myeloid cell mobilization and angiogenesis mediate tumor refractoriness to anti-VEGF therapy in mouse models. Proc Natl Acad Sci USA 106:6742–6747 (2009).

Antonio N, Bønnylykke-Behndtz ML, Ward LC, Collin J, Christensen IJ, Steiniche T, Schmidt H, Feng Y, Martin P: The wound inflammatory response exacerbates growth of pre-neoplastic cells and progression to cancer. EMBO J. 34:2219–2236 (2015).

Shen M, Jiang K, Sui Y, Xu Z, Cui H, Wang Y, Zhang H, Xu Z, Xu W, Ding Q, Chen Y: Characterization of CD66b and its relationship between immune checkpoints and their synergistic impact in the prognosis of surgically resected lung adenocarcinoma. Lung Cancer 160:84–91 (2021).

Sparrmann A, Bar-Sagi D: Ras-induced interleukin-8 expression plays a critical role in tumor growth and angiogenesis. Cancer Cell 6:447–458 (2004).

Jin Q, Esteva FJ: Cross-talk between the ErbB/HER family and the type I insulin-like growth factor receptor signaling pathway in breast cancer. J Mammary Gland Biol Neoplasia 13:485–498 (2008).

Di Maio M, Gridelli C, Gallo C, Shepherd F, Piantedosi FV, Cigolari S, Manzione L, Illiano A, Barbera S, Robbiano SF, Frontini L, Piazza E, Iannelli G Pietro, Veltri E, Castiglione F, Rosetti F, Gebbia V, Seymour L, Chioldini P, Perrone F: Chemotherapy-induced neutropenia and treatment efficacy in advanced non-small-cell lung cancer: A pooled analysis of three randomised trials. Lancet Oncol 6:669–677 (2005).

Bekes EM, Schweighofer B, Kupriyanova TA, Zajac E, Ardi VC, Quigley JP, Deryugina EI: Tumor-recruited neutrophils and neutrophil TIMP-free MMP-9 regulate coordinately the levels of tumor angiogenesis and efficiency of malignant cell intravasation. Am J Pathol 179:1455–1470 (2011).

Strell C, Lang K, Niggemann B, Zaneker KS, Entschenfeld F: Neutrophil granulocytes promote the migratory activity of MDA-MB-468 human breast carcinoma cells via ICAM-1. Exp Cell Res 316:138–148 (2010).

Singh J, Hamal D, Karmacharya A: Comparison of caudal Ropivacaine, Ropivacaine plus Ketamine and Ropivacaine plus Fentanyl administration for postoperative analgesia in children. J Nepal Paediatr Soc 32:210–215 (2012).

Nathan C: Neutrophils and immunity: Challenges and opportunities. Nat Rev Immunol 6:173–182 (2006).

Hazaﬁ A, Batool A, Ahmad S, Amjad M, Chaudhry SN, Asad J, Ghuman HF, Khan HM, Naeem M, Ghani U: Humanin: A mitochondrial-derived peptide in the treatment of apoptosis-related diseases. Life Sci 264 (2021).

Han Y, Yu Z, Wen S, Zhang B, Cao X, Wang X: Prognostic value of chemotherapy-induced neutropenia in early-stage breast cancer. Breast Cancer Res Treat 131:483–490 (2012).

Shaﬄ ME, Fridlender ZG: Tumour-associated neutrophils in patients with cancer. Nat Rev Clin Oncol 16:601–620 (2019).

Kwiatkowski K: The muslim people of desht-i qipchaq in ﬁfteenth-century prussia. Fear Loathing North Jews Muslims Medieval Balt Reg. Walter de Gruyter GmbH:141–170 (2015).

Youn J-I, Nagaraj S, Collazo M, Gabrilovich DI: Subsets of Myeloid-Derived Suppressor Cells in Tumor-Bearing Mice. J Immunol, 181: 5791–5802 (2008).

Chung AS, Wu X, Zhuang G, Ngu H, Kasman I, Zhang J, Vernes JM, Jiang Z, Meng YG, Peale F V., Ouyang W, Ferrara N: An interleukin-17-mediated paracrine network promotes tumor resistance to anti-angiogenic therapy. Nat Med 19:1114–1123 (2013).

Rayes T El, Catena R, Lee S, Stawowczyk M, Joshi N, Fischbach C, Powell CA, Dannenberg AJ, Altorki NK, Gao D, Mittal V: Lung inﬂammation promotes metastasis through neutrophil protease-mediated degradation of Tsp-1. Proc Natl Acad Sci USA 112:16000–16005 (2015).
Stark MA, Huo Y, Burcin TL, Morris MA, Olson TS, Ley K: Phagocytosis of apoptotic neutrophils regulates granulopoiesis via IL-23 and IL-17. Immunity 22:285–294 (2005).

Reiman JM, Kmieciak M, Manjili MH, Knutson KL: Tumor immunoediting and immunosculpting pathways to cancer progression. Semin Cancer Biol 17:275–287 (2007).

Houghton AMG, Rzymkiewicz DM, Ji H, Gregory AD, Egea EE, Metz HE, Stolz DB, Land SR, Marconcini LA, Kliment CR, Jenkins KM, Beaulieu KA, Mouded M, Frank SJ, Wong KK, Shapiro SD: Neutrophil elastase-mediated degradation of IRS-1 accelerates lung tumor growth. Nat Med 16:219–223 (2010).

Mollinedo F: Neutrophil Degranulation, Plasticity, and Cancer Metastasis. Trends Immunol 40:228–242 (2019).