MicroRNAs as Potential Clinical Biomarkers for Ovarian Cancer

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Ovarian cancer is a commonly diagnosed malignancy in women. When diagnosed at an early stage, survival outcomes are favourable for the vast majority, with up to 90% of ovarian cancer patients being free of disease at 5 years follow-up. Unfortunately, ovarian cancer is typically diagnosed at an advanced stage due to the majority of patients remaining asymptomatic until the cancer has metastasised, resulting in poor outcomes for the majority. While the molecular era has facilitated the subclassification of the disease into distinct clinical subtypes, ovarian cancer remains managed and treated as a single disease entity. Biomarkers are objectively measured such that they are informative of normal biological processes, pathological processes, or pharmacological responses to a therapeutic intervention. The incorporation of biomarkers into clinical practice can improve early detection of disease and aid the design of treatment regimens specific for individual patients. However, clinically established biomarkers for ovarian cancer lack robust reliability and specificity. MicroRNAs (miRNAs) are small (19–25 nucleotides), endogenous molecules which are integral to regulating gene expression. Aberrant miRNA expression profiles have been described in several cancers, and have been implicated to be useful biomarkers which may aid cancer diagnostics and treatment.

Keywords: ovarian cancer ; miRNA ; non-coding RNA ; personalised medicine

1. Ovarian Cancer: A Heterogenous Disease

Ovarian cancer is among the most commonly diagnosed gynaecological malignancies worldwide and is associated with high rates of mortality [1][2][3][4]. The poor oncological and survival outcomes observed in patients diagnosed with ovarian cancer is best explained by the subclinical growth of such tumours causing a delayed onset of non-specific symptoms [1][4], which is reflected in late diagnoses, when the cancer is at an advanced stage. Recent data from the National Cancer Registry Ireland illustrates that ovarian cancer is currently the fourth most common cause of cancer-related mortality in women in the Republic of Ireland [5].

The molecular era has progressed to recognise that ovarian cancer is a heterogenous disease made up of several behaviourally distinct intrinsic biological subtypes [6][7]. Such subtypes may be distinguished and characterised based on several parameters, including the anatomical origin of the cancer, the clinical behaviour of the disease, the biomolecular tumour profile, and the overall genetic instability of the disease [4]. The most common form of the disease is epithelial ovarian cancer, followed by germ cell and sex-cord-stromal ovarian, which together account for approximately 5% of cases [3]. Epithelial ovarian cancer can be further substratified into four pathologically distinct primary subtypes, which include serous (low-grade or high-grade), endometroid, clear cell and mucinous carcinoma [3]. In addition, malignant epithelial ovarian tumours may be subdivided into type I and type II tumour types, where type I represents the more indolent, less aggressive clinical subtype, and type II tumours behave aggressively and are typically associated with poor anticipated survival outcomes [4]. Typically, serous, endometrioid, clear cell and mucinous ovarian cancers which are low-grade are considered to represent type I disease, while high-grade serous tumours are classified to be type II disease. Importantly, high-grade serous ovarian cancer (HGSOC) is the most common form of the disease [6][8] and typically responds poorly to conventional therapeutic strategies, leading the disease to be responsible for up to 80% of all ovarian cancer-related deaths [8].

2. Biomarkers and Ovarian Cancer

A biomarker, a portmanteau of ‘biological marker’, is a characteristic that is objectively appraised to provide an indication of normal biological processes, pathological processes, or pharmacological responses to a therapeutic intervention [9]. Biomarkers are endogenous molecules which are detectable, measurable and quantifiable to indicate a state of disease. Diagnostic biomarkers can aid the earlier detection of disease while predictive and prognostic biomarkers can facilitate the

personalisation of treatment strategies [10]. Commonly evaluated examples of biomarkers relevant to malignancy include proteins and genetic material, including deoxyribonucleic acids (DNA), ribonucleic acids (RNA) and genetic alteration status [11][12][13]. Biomarker discovery is a well-established yet exciting field within the realm of translational research, and the development of novel oncological biomarkers remains at the forefront of translation research priorities. Such efforts aim to use non-invasive means to decipher novel diagnostic strategies, inform patient-specific prognosis, and monitor disease progression in the setting of metastatic disease [10].

Several biomarkers are currently used in clinical practice to aid cancer diagnosis and management. Cancer Antigen 125 (CA125) is a protein which is may be elevated to a detectable level in the circulation of up to 80% of patients diagnosed with epithelial ovarian cancer [1]. CA125 may be isolated from patient serum samples and quantified using antibody-based immunoassays, such as enzyme-linked immunosorbent assay (ELISA) [14]. While CA125 is a useful diagnostic biomarker, it also has utility in gauging therapeutic response to conventional treatment, with levels of the biomarker being measured and evaluated during treatment, to assess patient response to treatment. Notwithstanding, CA125 is limited by moderate sensitivity levels in the setting of early disease [1][15], unreliable measurements during certain physiological processes such as menstruation [16], and varying acceptable measurement levels in patients of a certain age, race, and body mass index [17]. Therefore, the identification of novel minimally invasive biomarkers to aid ovarian cancer diagnostics, inform prognosis and to gauge therapeutic response to treatment are imperative to improve the anticipated oncological outcomes for these patients.

3. MicroRNAs as Cancer Biomarkers

MicroRNAs (miRNAs) are a contemporary class of short non-coding RNA (sncRNA). The molecules are approximately 19 to 25 nucleotides in length and have been illustrated to play an integral role in regulating gene expression [18][19]. MiRNAs were first described by Lee et al. in 1993 when studying developmental timing of *Caenorhabditis elegans* [20], and the scientific understanding of the role of miRNA has exponentially grown in recent years, with aberrant miRNA expression profiles now understood to correlate with several diverse pathological processes, including oncogenesis [21][22][23][24]. MiRNAs regulate gene expression at a post-transcriptional level by binding to the 3′ or 5′ untranslated regions of target messenger RNA (mRNA), hindering mRNA expression through degradation or translation inhibition.

Aberrant miRNA expression profiles have been commonly observed within cancer cells, highlighting their potential as biomarkers and therapeutic targets in malignancy [2][11][19]. Thus, translational research efforts have focused on understanding the biomolecular mechanisms underpinning miRNA dysregulation and their impact upon oncogenesis. Identifying the idiosyncratic miRNA expression pattern specific to each cancer subtype has also been investigated to decipher novel molecular subtypes [25]. Therefore, it is plausible that miRNA expression profiles may potentially play several roles in ovarian cancer treatment, from expediting diagnosis, to designing more targeted treatment regimens, to monitoring patient-specific response to therapeutics [11][26].

MiRNAs can be divided up into two fundamental classes based on their target genes and oncological implications on tumour development [19]. Tumour suppressors act to silence genetic information implicated in uncontrolled proliferation and subsequently halt cancer progression [27]. Intuitively, tumour suppressor miRNAs are typically downregulated in cancer cells, triggering potentially uncontested tumourigenesis. The second class, oncogenic miRNAs (typically described as oncogenes or oncomiRs), are molecules which promote cancer development through increasing expression of cancer inducing genes, thereby contributing to oncogenesis. Conversely to tumour suppressor miRNAs, oncomiRs are classically upregulated in the setting of malignancy [27].

4. MiRNAs as Therapeutic Agents

The increased understanding of the regulatory roles of miRNAs presents these endogenous molecules as therapeutic tools with significant potential in the targeted treatment of cancer [28]. Several strategies have been developed to interfere with the expression of specific oncomiRs and tumour suppressor miRNAs. Sandwich RNAi inhibition involves simultaneous targeting of an oncomiR by a combination of siRNA- and miRNA-based technologies [28]. This dual targeting has demonstrated enhanced therapeutic efficiency. Nishimura et al. targeted the expression of EphA2, an oncogenic protein expressed in ovarian cancer, using siRNA and miR-520d-3p which resulted in robust depletion of the protein levels [29]. MiRNA sponges are synthetic oligonucleotides which have been designed to have high affinity for target miRNA molecules [30]. MiRNA sponges act as competitive inhibitors with specific oncomiR silencing capabilities. Small molecule miRNA inhibitors (SMIRs) have been designed to directly bind to target miRNAs thereby interfering with their normal mechanisms of gene silencing [31]. Conversely, RNA restoration therapy has also been explored as a potential therapeutic strategy. MiRNA mimics, synthetic RNA duplexes which are designed to resemble endogenous miRNAs, have been

transiently transfected into cells and have been successful in upregulating target gene expression [32]. Exosomes, nanoparticles, lentivirus and plasmid expression vectors are some of the delivery mechanisms explored for transduction of these miRNA-based therapeutics to target cells [28].

5. Tumour Suppressor and OncomiRs Associated with Ovarian Cancer

Tumour suppressors act to silence genetic information and subsequently attempt to prevent tumour progression. Several tumour suppressor miRNAs have been identified and their roles in the development of several cancers are beginning to be unravelled. For example, miRNA expression profiling has demonstrated that the miR-15/16 cluster and the miR-34 family are commonly under expressed in colorectal and prostate carcinoma [33]. Moreover, miR-101 has been illustrated to be involved in several biological processes associated with cancer development including tumour proliferation, angiogenesis and metastasis [34]. MiR-101 has been implicated to be typically downregulated in cancerous tissues, and plays a role in silencing multiple target oncogenes, such as *SOX2* [35], *DNMT3A* [36] and *EZH2* [37]. EZH2 is a catalytic subunit of polycomb repressive complex 2 (PRC2) and plays a major role in regulating gene expression by catalysing the trimethylation of H3 lysine 27 (H3K27) [34][37]. Epithelial ovarian cancer cell viability has been shown to be dependent on EZH2 expression, and therefore, EZH2 inhibition, is a promising targeted therapeutic strategy [38], highlighting the potential of miR-101 in the treatment of epithelial ovarian cancer. This dependency however is seen in certain mutational contexts, further emphasising the importance of understanding ovarian cancer heterogeneity [38].

Members of the let-7 family of miRNAs play essential roles in regulating development and cellular differentiation [39][40][41]. Therefore, it is unsurprising that the aberrant expression of let-7 miRNAs is associated with cancer. There are ten members of the let-7 family, namely, let-7a, let-7b, let-7c, let-7d, let-7e, let-7f, let-7g, let-7i, miR-98 and miR-202 [41], and dysregulation of several let-7 miRNAs has been reported in a range of cancer types [41][42][43][44]. In the majority of these cases, expression of let-7 miRNAs is decreased, which has been shown to result in elevated levels of target oncogenic proteins such as RAS, Myc, and LIN28 [39]. Let-7g was previously shown to be significantly downregulated in the serum and tumour tissue of epithelial ovarian cancer patients [45]. The exact role of let-7 miRNAs in ovarian cancer development however remains ambiguous, as overexpression of let-7 family members has also been demonstrated in the setting of malignancy [39]. Nonetheless, this family of miRNAs has significant potential as diagnostic and prognostic biomarkers. In addition, there has been accumulating evidence that let-7 miRNAs could be utilised in potential therapeutic strategies [46].

The highly conserved miR-200 family is made up of miR-200a, miR-200b, miR-200c, miR-141 and miR-429, and is frequently studied in cancer biology [47]. A meta-analysis of miRNA expression signatures in epithelial ovarian cancer identified miR-200a and miR-200c as the two most highly dysregulated miRNAs in ovarian cancer [48]. Mir-200a and miR-200c were significantly upregulated in epithelial ovarian cancer cases. This overexpression of miR-200a/c is correlated with improved outcomes of epithelial ovarian cancer patients [48]. The sensitivity and specificity of miR-200a/c was also analysed, which provided further support for their potential use as diagnostic biomarkers. Although preliminary, findings such as these warrant further investigation as oncomiRs could serve as useful diagnostic and prognostic biomarkers for the early detection of ovarian cancer. The expression levels of a panel of seven circulating miRNAs with a known association with cancer in the serum of epithelial ovarian cancer patients were investigated [49]. Among these, miR-25 and miR-93 were significantly downregulated, while miR-7 and miR-429 were significantly upregulated in the cancer patient samples compared to the serum of the healthy controls. Furthermore, a positive correlation between miR-429 and CA-125 levels was observed in ovarian cancer patients, highlighting its potential as a diagnostic and prognostic ovarian cancer biomarker [49].

6. Using MiRNAs to Differentiate between Female Cancers

Previous researchers have focused their efforts into identifying novel diagnostic biomarkers which can aid the early detection of cancer, as cancer diagnosis at an early stage is key to ensuring successful treatment and enhancing patient outcomes. This is particularly important in cases of ovarian malignancies, as symptoms are relatively non-specific, with presentations usually reserved until the cancer has progressed to an advanced stage. The management of metastatic ovarian cancer is challenging to the oncologist as the disease typically becomes more resistant to treatment. Thus, the application of miRNA panels (rather than just a single miRNA type) may yield more informative information in aiding cancer diagnostics. Expression patterns of 25 clinically relevant miRNAs were analysed in breast, endometrial and ovarian cancer cells [50]. It was outlined that by comparing miRNA expression patterns across the different cell types, differentiation between cancer subtypes could be successfully achieved. The most significant findings relating to ovarian cancer miRNAs were that let-7b, miR-21, and miRNAs from the miR-30 family were upregulated in ovarian cancer cells relative to breast cancer cells. Furthermore, it was detailed that miRNA expression patterns could potentially distinguish ovarian cancer cells from endometrial cancer cells. MiR-92a, miR-106a and miR-200b were upregulated in endometrial

cancer cells compared to ovarian, and conversely miR-222 was upregulated in ovarian cancer cells compared to endometrial cancer cells [50].

7. Using MiRNAs to Determine Ovarian Cancer Subtype

The prescription of generic treatment regimens in ‘blanket’ fashion for all patients with ovarian cancer opposes the dogma of precision oncology [51]. Identifying miRNA signatures specific to ovarian cancer subtypes would aid in clinical diagnosis and have a direct impact on choice of treatment. Efforts have been made to identify miRNA expression patterns which are unique to ovarian cancer subtype in an attempt to identify novel diagnostic and prognostic biomarkers. In one particular study, miRNAs of the miR-192/215 family (miR-192, miR-194, miR-215), were found to be significantly upregulated in mucinous carcinoma tissue, and downregulated in each other subtype [52]. The exact biological pathways of the miR-192/215 family in ovarian cancer are yet to be uncovered. miR-9 was also identified as a potential diagnostic biomarker and therapeutic target for ovarian clear cell carcinoma [53]. In comparison to HGSOC, significantly higher expression of miR-9 was observed in clear cell carcinoma cells. Another study highlighted the potential of using miRNAs to differentiate between different subtypes of epithelial ovarian cancer [54]. These results illustrate the importance of miRNA expression levels to highlight variety between the different subtypes of the disease, supporting the concept that ovarian cancer is not a homogenous disease. Inversely, ovarian cancer should be divided into clinical and therapeutically distinct molecular subtypes with targeted therapies specific to inhibit the biological activity of the tumour, while minimising the treatment associated toxicities associated with robust chemotherapy prescription.

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